THE USE OF AN EVIDENCE BASED APPROACH TO GUIDE OPTIMAL SURGICAL MANAGEMENT OF COLORECTAL LIVER METASTASES

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Declaration of own work

I, Dr Constantinos Simillis confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. It should be noted that the scientific studies presented in this thesis reflect the contributions of a team of researchers, and I have conducted most steps of study design, data collection, data analysis, and interpretation of the results.

Signature

ACKNOWLEDGEMENTS

I would like to thank my supervisors Mr Kurinchi Gurusamy and Professor Brian Davidson for their constant support and inspiring guidance throughout the course of this thesis.

This thesis is dedicated to the memory of my beloved father, Panayiotis Simillis, who passed away while I was writing this thesis. Father, I miss you so much, and I am grateful for every moment we spent together. It is your shining example that I try to emulate in all that I do.

Also, dedicated to my mother Maroulla, my brother Michalis, and to Thalia for their unconditional love and support.

ABSTRACT

The aim of this thesis was to validate the optimal surgical management of colorectal liver metastases (CLM) by using an evidence based approach.

A meta-analysis comparing combined and sequential resection for synchronous CLM demonstrated that combined resection is associated with reduced hospital stay and with comparable perioperative mortality and morbidity, operative blood loss, and survival rates as sequential resection. Nevertheless, combined resection was associated with lower metastatic disease severity compared to sequential resection.

A meta-analysis assessed liver resection for CLM in the presence of hepatic lymph node involvement and demonstrated that survival rates are lower in node positive disease patients compared to node negative disease patients, irrespective of whether the positive disease nodes were detected by routine or selective lymphadenectomy, or whether nodal involvement was microscopic or macroscopic.

A network meta-analysis comparing different treatment strategies aiming to decrease operative blood loss found no difference in mortality, length of hospital stay or ITU stay between the treatment strategies. The use of radiofrequency dissecting sealer resulted in more serious adverse events compared to the clamp-crush method in the absence of vascular occlusion and fibrin sealant. Simple methods, such as clamp-crush method, gave overall equivalent outcomes to methods which require special equipment.

Not reporting the period of follow-up was investigated as a potential source of study bias. Overall analysis did not identify a significant difference in mortality and disease recurrence, but sensitivity analysis of more recent reviews and larger reviews showed that the trials reporting the period of follow-up had a significantly lower hazard ratio for disease recurrence compared to trials not reporting the period of follow-up.

A network meta-analysis comparing interventions aiming to decrease ischaemia-reperfusion injury during liver resection, demonstrated that ischaemic preconditioning resulted in fewer serious adverse events, lower operative blood loss, fewer transfusion proportions, and shorter operative time.

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LIST OF ABBREVIATIONS

CASH	Chemotherapy-Associated Steatohepatitis
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Intervals
CLM	Colorectal Liver Metastases
CrI	Credible Intervals
CT	Computed Tomography
CUSA	Cavitron Ultrasonic Surgical Aspirator
DIC	Deviance Information Criteria
DSU	Decision Support Unit
EBM	Evidence-Based Medicine
FDG	18-fuorodeoxyglucose
FLR	Future Liver Remnant
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCC	Hepatocellular Carcinoma
HPB	HepatoPancreatoBiliary
HR	Hazard Ratio
IR	Ischaemia-Reperfusion
ITU	Intensive Therapy Unit
lnHR	natural logarithm of Hazard Ratio
MH	Mantel-Haenszel
MD	Mean Difference
MDT	Multidisciplinary Team
min	minutes
mL	millilitres
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Clinical Excellence
NOS	Newcastle-Ottawa Scale
NRR	Non-Randomised Retrospective
OR	Odds Ratio
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography - Computed Tomography
PRISMA	Preferred Reporting Items for systematic Reviews and Meta-Analyses
PVE	Portal Vein Embolisation

RCT	Randomised Controlled Trial
SD	Standard Deviation
SE	Standard Error
SE(lnHR)	standard error of natural logarithm of Hazard Ratio
SEC	Sinusoidal Endothelial Cell
UK	United Kingdom
US	United States (of America)

CHAPTER 1

INTRODUCTION

1.1 COLORECTAL LIVER METASTASES

Cancer is one of the leading causes of death worldwide, accounting for 8.2 million deaths in 2012.[1] Worldwide, colorectal cancer is the second most common cancer in women (614,000 cases diagnosed every year, 9.2% of all cancer diagnoses),[1] and the third most common in men (746,000 cases,10.0% of all cancer diagnoses).[1] Every year, approximately 1.3 million people are diagnosed with colorectal cancer.[1, 2] Almost 55% of all cases of colorectal cancer are diagnosed in the more developed countries.[1] Importantly, colorectal cancer is the fourth most common cause of cancer death worldwide after lung, stomach, and liver cancer,[3] resulting in about 694,000 deaths every year.[3]

In England and Wales, colorectal cancer is the second most common cancer after lung cancer, in terms of both incidence and mortality.[4] Each year, over 30,000 new cases of colorectal cancer are diagnosed in England and Wales, and colorectal cancer is registered as the underlying cause of death in about half this number.[4] In the United States (US) colorectal cancer is the third most prevalent form and has the second highest mortality rate of any cancer.[5] It is estimated that 142,820 new cases and 50,830 deaths occurred due to colorectal cancer in 2013 in the US.[6]

Approximately 50% to 60% of patients with colorectal cancer will develop colorectal liver metastases (CLM) during their lifespan.[7-9] In some people with colorectal cancer, the liver spread is present at the time of diagnosis of the primary tumour (synchronous metastases) and in others, the liver spread is identified at a later stage (metachronous metastases). Approximately 15% to 25% of patients with colorectal cancer have detectable liver metastases at the time of presentation (synchronous CLM) and a further 20% to 25% of patients will develop metastases during the course of their disease (metachronous CLM).[10-13]

The presence of CLM is a poor prognostic indicator with the median survival for untreated disease ranging between six to twelve months.[14, 15] Removal of part of the liver to which the cancer has spread (liver resection), the only curative option for people with CLM, is indicated in the 20% to 30% of patients in whom the metastases are confined to the liver.[7, 16-18] Five-year survival for patients with CLM who undergo liver resection, ranges between 32 and 58%,[19-27] and 10-year survival ranges between 22 and

28%.[20-22, 25-27] Table 1.1. shows the 5-year and 10-year survival for patients with CLM who underwent liver resection with curative intention from studies published in the literature.

Table 1.1: Five-year and 10-year survival for patients with CLM who underwent liver resection with curative intention from studies published in the literature (NR=not reported).

Author	Year	Participants	5-year survival	10-year survival
Gayowski *et al.*[23]	1994	204	32%	NR
Scheele *et al.*[26]	1995	350	39%	24%
Fong *et al.*[21]	1999	1001	37%	22%
Choti *et al.*[20]	2002	226	40%	26%
Abdalla *et al.*[19]	2004	190	58%	NR
Pawlik *et al.*[24]	2005	557	58%	NR
Wei *et al.*[27]	2006	423	47%	28%
Fortner *et al.*[22]	2009	293	35%	24%
Pulitano *et al.*[25]	2010	309	32%	23%

For patients with unresectable CLM, modern systemic neoadjuvant chemotherapy can be used to downsize the liver metastases so that an R-0 resection (negative tumour margins) is possible, and allows approximately 12.5% of patients with unresectable CLM to be rescued by liver surgery.[16, 28, 29] Furthermore, the use of modern adjuvant chemotherapy for patients with CLM who underwent liver resection with curative intent, may result in improvement of disease-free survival and overall survival.[30-34] Along with the benefits of chemotherapy, chemotherapeutic agents can cause liver parenchymal injury, known as chemotherapy-associated steatohepatitis (CASH), which results in increased postoperative morbidity in patients who had undergone hepatectomy.[35, 36]

The imaging modalities most frequently used for detection, staging, and determining resectability of CLM are computed tomography (CT), magnetic resonance imaging (MRI) which is liver specific, and 18-fuorodeoxyglucose (FDG) positron emission tomography CT (PET-CT) which is patient specific.[37-40] The use of all three imaging modalities as a triple liver assessment is associated with low futile laparotomy rates, and is considered routinely in all patients being considered for hepatectomy.[37-39] A study by Dunne *et al.* suggested that with modern imaging, the potential yield of staging laparoscopy is low, and that staging laparoscopy should not be used routinely.[37] According to Yip *et al.*, assessment of initial CT, followed by a multidisciplinary team (MDT) discussion of patients with CLM, with subsequent PET-CT and MRI imaging thereafter (hybrid model), is associated with the shortest time-to-decision and lowest cost.[39]

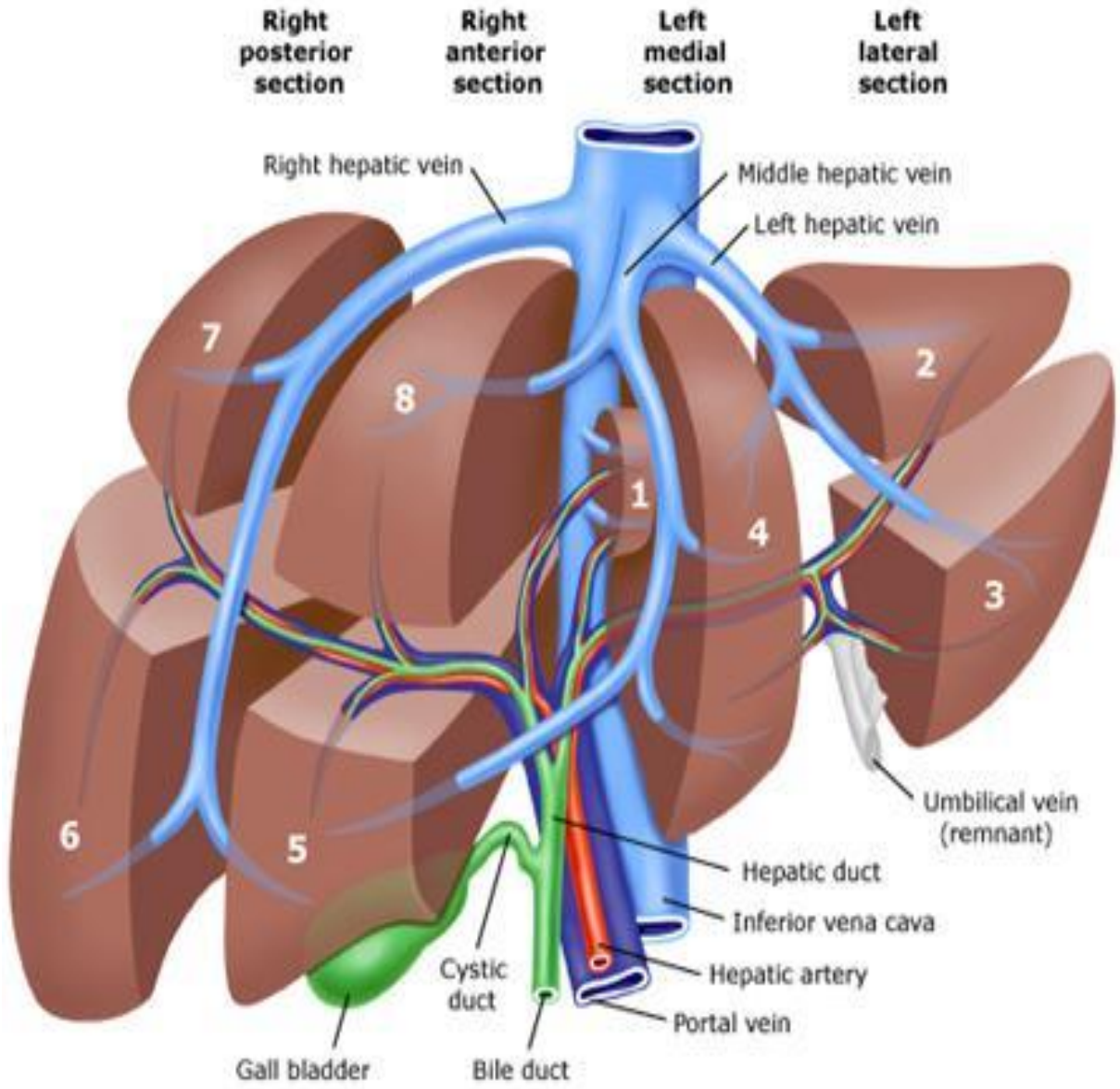
Patients suffering with CLM should be managed by a MDT at centres specialised in the diagnosis, staging, and oncological and/or surgical treatment of CLM. Management of patients suffering with CLM without the involvement of a specialist liver MDT, or tumour board, may lead to inappropriate management of these patients and is associated with lower resection rates, and patients being inappropriately denied potentially curative treatments.[39, 41] Consequently in the United Kingdom (UK) it is now seen as the standard of care that a specialist liver surgeon and specialist liver MDT should assess all patients suffering with liver limited metastases from colorectal cancer.[39, 42]

1.2 LIVER RESECTION

Liver resection, or hepatectomy, refers to removal of part of the liver. The liver is a common site for both primary and secondary malignancy. Hepatic resection is the main curative treatment for primary and metastatic cancer of the liver. Unfortunately, only 10 to 20% of patients are candidates for this treatment.[43, 44] For the remaining patients the main alternative treatment would be palliative chemotherapy. Tumour ablation (e.g. radiofrequency ablation, microwave ablation, high-intensity focused ultrasound, cryoablation, chemical ablation, selective internal radiotherapy treatment) has emerged as a promising alternative treatment, and in a few cases may downstage patients to allow a potentially curative hepatectomy.[43]

The most common reasons for liver resection are CLM, hepatocellular carcinoma (HCC), cholangiocarcinoma, and benign liver tumours.[45, 46] Anatomically, the liver can be subdivided into eight segments as described by Couinaud,[47] based on the fact that each has its own vascular inflow, outflow and biliary as well as lymphatic drainage. In the centre of each segment there is a branch of the portal vein, hepatic artery and bile duct; in the periphery of each segment there is vascular outflow through the hepatic veins.[47] Each Couinaud segment can be removed individually, or in combination, by right hemi-hepatectomy (Couinaud segments 5 to 8), left hemihepatectomy (segments 2 to 4), right trisectionectomy (segments 4 to 8), or left trisectionectomy (segments 2 to 5 and 8 ± 1) (see Figure 1.1).[48] Although every liver resection is considered major surgery, major hepatectomy is defined as a right or left hemihepatectomy (or lobectomy), or extended hemihepatectomy (or extended lobectomy), or resection of three or more liver segments according to Couinaud.[47]

Figure 1.1: Anatomically, the liver is subdivided into eight segments as described by Couinaud. In the centre of each segment there is a branch of the portal vein, hepatic artery and bile duct; in the periphery of each segment there is vascular outflow through the hepatic veins (figure by Schiff *et al.*).[49]



Liver resection is feasible, and safely performed, as an open operation, laparoscopically, or with a robot. At first, laparoscopic liver resection was looked upon with scepticism because of concerns regarding parenchymal transection, bleeding control, bile leakage, incomplete tumour resection, air embolism, and difficult retraction and liver mobilization during laparoscopy with the risk of injuring major adjacent structures.[50-54] Nevertheless, studies comparing laparoscopic versus open liver resections have shown that laparoscopic hepatectomy is a safe and feasible option, and demonstrated no significant difference in operating time, postoperative adverse events, extent of oncologic clearance, disease recurrence, or overall survival between laparoscopic and open hepatectomy.[53, 55-57] Furthermore, laparoscopic liver resection was shown to result in significantly lower operative blood loss, fewer patients requiring blood transfusion, and shorter length of hospital stay.[53, 56, 57] Moreover, studies comparing laparoscopic versus robotic liver resection demonstrated no difference between the two minimally invasive techniques in operative and postoperative outcomes (as measured by intraoperative blood loss, transfusion rate, negative margin rate, postoperative liver function tests, postoperative intensive care unit admission rate, length of hospital stay, and 90-day mortality).[58-60] Robotic hepatectomy resulted in significantly longer operative times[59] and higher costs;[60] however, it also allowed for an increased percentage of major hepatectomies to be performed in a purely minimally invasive fashion.[59]

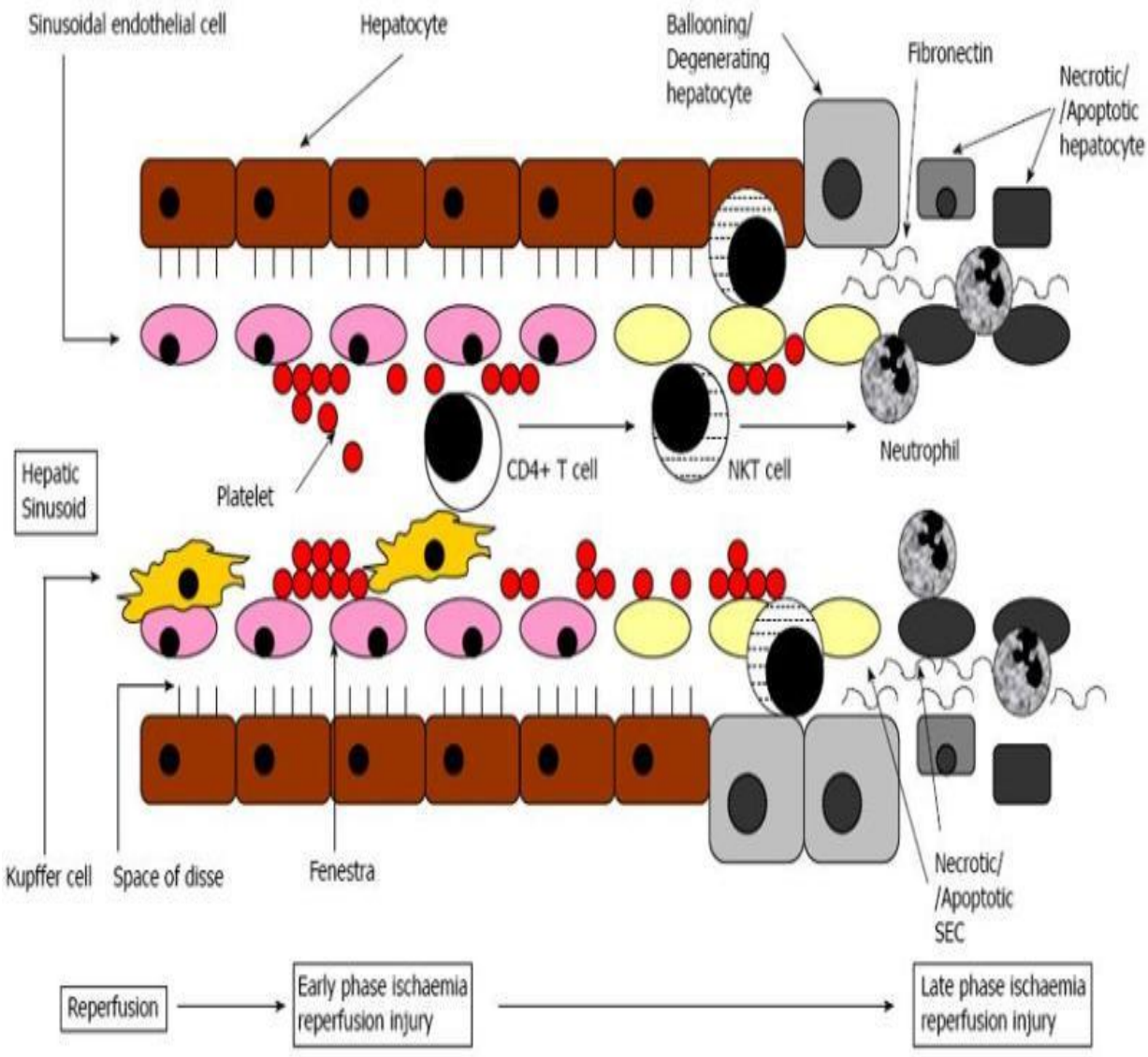
Over the years, indications for liver resection have been broadened and the number of liver resections performed has increased. The number of liver resections performed in the UK has more than doubled over the last 10 years, from around 1000 in 2003, to around 2400 liver resections in 2013.[61, 62] This increase is probably due to the existence of cancer networks, regional referral guidelines, MDTs, and published results on surgical outcomes. It is also due to advances in diagnostic and imaging techniques, operative and anaesthetic methods, neo-adjuvant therapy, improvements in the perioperative care, better patient selection, and better understanding of hepatic anatomy resulting in anatomically based resections.[45, 46, 63] Despite these advances, liver resection remains a major surgical procedure with significant mortality of around 4% and morbidity of around 40%.[45, 46, 63]

Intraoperative haemorrhage remains one of the major risks during liver resections, and operative blood loss and perioperative blood transfusion are two of the most important

factors affecting perioperative morbidity and mortality.[45, 46, 64, 65] Therefore, minimising blood loss is of major importance, and methods of hepatic vascular occlusion have been developed over the years to reduce the bleeding during elective liver resection.[66] By using different techniques to control the hepatic blood inflow and outflow the surgeons manage to decrease the blood loss during hepatic resections resulting in decreased need for blood transfusion, and lower morbidity and mortality. Clamping of the portal pedicle (Pringle manoeuver, i.e. clamping of the hepatic artery and portal vein) is the oldest and commonest method of hepatic vascular occlusion and can be performed either continuously or intermittently during the parenchymal resection.[67-69] Also, different methods of liver transection have been used to reduce blood loss, such as the clamp-crush method, the Cavitron ultrasonic surgical aspirator, or the radiofrequency dissecting sealer. In addition, different methods of management of the cut surface of the liver have been used, such as the use of fibrin sealant, argon beamer, or electrocautery and suture material.[66, 70]

Hepatic vascular occlusion aims to decrease operative blood loss, but, along with mobilization and retraction of the liver during surgery, it causes ischaemia and reperfusion (IR) injury to the liver. Control of the hepatic blood inflow and outflow have allowed major hepatic resections to be carried out with decreased blood loss but it has done so at the expense of liver damage from warm ischaemia and reperfusion. IR injury of the liver involves a number of mechanisms. Ischaemia followed by reperfusion results in the activation of Kupffer cells (liver macrophages) and polymorphonucleocytes, production of reactive oxygen species and pro-inflammatory cytokines, and induction of endothelial cell surface adhesion molecules, resulting in microvascular hypo-perfusion and liver parenchymal damage.[71-74] Figure 1.2, taken from a study by Datta *et al.*,[75] is a schematic diagram of the cellular mechanisms involved during IR injury of the liver. According to Datta et al., IR injury is initiated by reactive oxygen species which cause direct cellular injury and sinusoidal perfusion failure from platelet plugging.[75] Then a cascade of molecular mediators is activated leading to microvascular and acute inflammatory changes. Kupffer cells activate CD4+ T-cells that activate natural killer T-cells which cause sinusoidal endothelial cells (SEC) and hepatocyte injury, followed by neutrophil activation, adhesion and transmigration, resulting in more necrosis and/or apoptosis of SEC and hepatocytes.[75]

Figure 1.2: A schematic diagram of the cellular mechanisms involved during IR injury of the liver. IR injury is initiated by reactive oxygen species which cause direct cellular injury and sinusoidal perfusion failure from platelet plugging. Then a cascade of molecular mediators is activated leading to microvascular and acute inflammatory changes. Kupffer cells activate CD4+ T-cells that activate natural killer T-cells which cause sinusoidal endothelial cells (SEC) and hepatocyte injury, followed by neutrophil activation, adhesion and transmigration, resulting in more necrosis and/or apoptosis of SEC and hepatocytes (taken from Datta et al.[75]).



Patients with cirrhotic liver are more sensitive to IR injury than patients with normal liver.[76, 77] Many methods have been used to decrease IR injury during liver resection, including hypothermia,[78] mechanical interventions such as ischaemic preconditioning,[67, 68, 76, 79, 80] ischaemic post-conditioning,[81] and pharmacological interventions such as anti-oxidants,[82] prostaglandins,[83] steroids,[84, 85] different anaesthetic agents,[86, 87] treatments to increase hepatocellular glycogen,[88, 89] and treatments affecting the cardiovascular system.[90, 91] These interventions can be used alone or in combination. Ischaemic preconditioning is the mechanism by which brief periods of ischaemia followed by reperfusion of the organ results in the ability of the organ to withstand a subsequent prolonged period of ischaemia.[92] Ischaemic preconditioning may be direct (i.e. hepatic vascular occlusion for brief periods before liver resection) or remote (i.e. brief episodes of ischaemia–reperfusion applied in distant tissues or organs to render the liver resistant to subsequent sustained episode of ischaemia).[93, 94]

Before major hepatic resection, assessment of the anticipated functional remnant liver is essential in order to avoid postoperative hepatic insufficiency. In a study by Mullen *et al.*, the hepatic insufficiency-related mortality rate was 2.8%.[95] Although the risk of postoperative hepatic insufficiency is influenced by multiple factors, a key determinant to ensuring adequate functional remnant liver is preoperative measurement of the future liver remnant (FLR) volume.[96-99] Preoperative volumetric analysis of the anticipated FLR is an essential component of surgical planning and the expected remnant liver volume appears to be a good predictor for liver failure in patients who undergo hepatectomy.[100, 101] The volume of the FLR correlates with FLR function and postoperative outcome.[100, 102-104] Careful patient selection based on volumetric analysis in major hepatectomy cases ensures that sufficient functional liver parenchyma remains and, consequently, minimizes the risks of postoperative hepatic insufficiency and mortality.[99-101]

Because CT is routinely performed for both tumour staging and preoperative surgical planning, 3-dimensional CT volumetry has become the standard technique for measuring FLR.[100, 101, 104, 105] CT measurements of preoperative FLR volume have been found to correlate linearly with actual volumes of the resected specimens.[98, 100, 106] Using standardized liver volumetry, guidelines have been proposed regarding the minimal amount of functional liver necessary for successful hepatic resection, based on multiple studies demonstrating a correlation between standardised FLR and

postoperative outcome.[100, 104, 107-109] Minimum standardised FLR thresholds for safe hepatectomy have been identified as 20% in patients with normal livers, 30% in those with chemotherapy-related liver injury, and 40% in those with chronic liver disease.[100]

When the anticipated FLR is estimated to be too small for major liver resection, preoperative portal vein embolization (PVE) is indicated.[99, 100, 106] PVE reduces the size of the liver to be resected and increases the volume of the remnant liver by inducing hypertrophy of the non-embolized liver, allowing a safer hepatectomy.[96-98] The minimum standardized FLR and indications for PVE are tailored to each patient and depend on many factors, including the complexity of the anticipated resection, simultaneous procedures, patients' comorbidities, and underlying liver disease.[97, 100] The hypertrophy of FLR induced by PVE has beneficial effects on the postoperative course in patients with normal liver and in patients with chronic liver disease.[97, 100, 108]

For patients with synchronous liver metastases, traditionally most surgeons perform a 'sequential' resection, whereby the primary colorectal tumour is resected first followed by liver resection at a later stage.[110] More recently, surgeons have started performing 'combined' resections whereby the primary tumour and liver resection are performed concurrently.[11] Nevertheless, there remain concerns regarding combined resections about both the safety and the long-term oncological effects, and surgeons perform combined resections in a selected group of patients with an easily resectable primary, limited metastatic disease, and few comorbidities.[111-113]

Liver resection for CLM in the presence of hepatic lymph node involvement is controversial. Hepatic node involvement detected pre-operatively or during surgery is considered as a poor prognostic factor[114-116] and has been labelled as a contraindication to surgery.[115] Both macroscopic and microscopic lymph node involvement have been shown to have a negative impact on survival.[116-119] Nevertheless, with significant improvements in perioperative cross sectional imaging, patient selection for liver resection, the safety of surgical techniques and chemotherapeutic agents in recent years, the previous contraindication to surgery in patients with hepatic node involvement is being challenged.

After liver resection for CLM, patients need to be followed up for a period of years in order to properly assess their response to treatment. Survival and disease recurrence are

the main outcomes when comparing treatments for CLM, and long period of follow-up is required to assess these outcomes. The optimal follow-up period in comparing treatments in patients with CLM with regards to survival benefit is not known. While following these patients for a long period will provide definitive answers, a long follow-up period will increase the trial costs and delay the adoption of treatment whereas a short period of follow-up may not be informative.

1.3 EVIDENCE BASED APPROACH

Evidence-based medicine (EBM) is the application of scientific method and the use of evidence from well designed and conducted research in healthcare decision-making.[120] EBM advocates that to the greatest extent possible, decisions and policies should be based on scientific evidence, not just the beliefs of healthcare practitioners, experts, or administrators.[120] EBM promotes the use of formal, explicit methods to analyse scientific evidence and make it available to healthcare decision makers.[120] Sackett *et al.* defined evidence-based medicine as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research."[121] Greenhalgh provided a definition emphasizing the use of quantitative methods in EBM: "the use of mathematical estimates of the risk of benefit and harm, derived from high-quality research on population samples, to inform clinical decision-making in the diagnosis, investigation or management of individual patients".[122]

The five steps of EBM in practice were first described in 1992,[123] and a consensus statement developed by the delegates at the second international conference of Evidence-Based Health Care Teachers and Developers held in Sicily in September 2003 summarised the five steps of EBM as shown in Table 1.2.[124]

Table 1.2: The five steps of EBM.[124]

1. Translation of uncertainty to an answerable question
2. Systematic retrieval of best evidence available
3. Critical appraisal of evidence for validity, clinical relevance, and applicability
4. Application of results in practice
5. Evaluation of performance

To help identify the best evidence, the levels of evidence in the medical literature have been categorised according to the strength of their freedom from the various biases that beset medical research. An example of a system for grading evidence for a treatment is the Oxford (UK) Centre of Evidence Based Medicine Levels of Evidence shown in Table 1.3.[125]

Table 1.3: The Oxford (UK) Centre of Evidence Based Medicine Levels of Evidence.[125]

1a: Systematic reviews (with homogeneity) of randomised controlled trials
1b: Individual randomised controlled trials (with narrow confidence interval)
1c: All or none randomised controlled trials
2a: Systematic reviews (with homogeneity) of cohort studies
2b: Individual cohort study or low quality randomised controlled trials (e.g. <80% follow-up)
2c: "Outcomes" Research; ecological studies
3a: Systematic review (with homogeneity) of case-control studies
3b: Individual case-control study
4: Case-series (and poor quality cohort and case-control studies)
5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

The current system used for grading the level of evidence is the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[126] The GRADE working group began in 2000 with the aim to develop a common, sensible approach to grading quality of evidence and strength of recommendation. According to the GRADE working group, it is essential to know whether a recommendation is strong (we can be confident about the recommendation) or weak (we cannot be confident), because poor quality evidence can lead to recommendations that are not in the patients' best interests.[126] Some grading systems are based on study design alone without explicit consideration of other important factors in determining quality of evidence, and other systems are excessively complex.[126] The GRADE system categorizes the quality of the evidence as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on

our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and very low (any estimate of effect is very uncertain). The GRADE working group developed a software application that facilitates the use of the approach and allows the development of summary tables.[126]

Because the randomised trial, and especially the systematic review of several randomised trials, is so much more likely to inform us and so much less likely to mislead us, it has become the "gold standard" for judging whether a treatment does more good than harm.[121] If several studies address the same clinical question, the evidence may be summarised in 'evidence tables', or the results of the studies may be synthesized in the form of meta-analyses.[127] If the studies have similar design and assess the same quantitative outcomes, a meta-analysis can be performed to statistically combine and compare quantitative results from several similar studies and produce effect estimates for each outcome. If the exposure and/or outcome differ too much between studies, it may not be possible to conduct a meta-analysis combining results from individual studies, and the researchers may do a systematic review only and produce the results as 'evidence tables'. Systematic reviews or meta-analyses of the published medical literature is a major part of the evaluation of various medical treatments and are important in deciding the medical or surgical management of patients.

Liver surgery can cure metastatic colorectal cancer although in only a small proportion (10 to 20%) of patients who are eligible for surgery.[43, 44] However, with advances in technique and better understanding of the natural history of the condition, more patients can have safe, potentially curative surgery. The management of colorectal liver metastases has changed significantly over the years due to major advances in technology, radiological imaging, surgery, and chemotherapy. There is a vast amount of research available on this subject offering opportunities for systematic reviews and meta-analyses to be performed.

There are many unanswered questions in the surgical management of CLM. Liver resection is a major surgery with significant risk of mortality and morbidity, with excessive blood loss from the cut surface of the liver being a major reason. Various methods have been attempted to decrease the blood loss and hence the complications

during liver resection. These methods include temporary occlusion of the blood vessels that supply the liver at the time of resection; different methods of liver transection; and different methods of management of cut surface of the liver. However, the benefit or efficacy of these different methods is not known.

In addition, blocking the blood vessels supplying the liver in order to reduce haemorrhage during resection, can affect the liver that is not removed by causing IR injury, resulting in significant postoperative morbidity and mortality. Many interventions have been attempted to decrease the damage to the remnant liver including hypothermia,[78] mechanical interventions such as repeated cycles of brief blockage of blood supply to the liver which 'conditions' or 'primes' the liver cells to withstand prolonged periods of blockage of blood supply,[67, 68, 76, 79, 80], and medicines such as anti-oxidants[82] or steroids.[84, 85] Whether any of these interventions to decrease IR injury during liver resection are beneficial is not known, and currently, none of these interventions is considered standard practice.

Apart from the method of performing liver resection, various other controversies related to the surgical management of CLM exist. In people with synchronous liver metastases, the options are bowel resection and liver resection at the same time (simultaneous liver and bowel resection), or bowel resection initially followed by liver resection at a later time (sequential resection). The dilemma is because both bowel resection and liver resection are major operations and performing both simultaneously may be more challenging than performing each operation separately. Another major controversy is whether liver resection should be performed in patients with hepatic lymph node metastases. Furthermore, it is important to identify potential sources of bias in comparative trials comparing treatments for CLM, for example, whether not reporting the follow-up in a comparative trial is a possible source of bias.

This thesis includes a series of systematic reviews or meta-analyses, attempting to find answers to the above questions based on the current evidence in the medical literature. Network meta-analysis will also be used, a recent development in meta-analysis. Network meta-analysis is performed when multiple interventions are available for the treatment of a disease and have been compared in different head-to-head comparisons. No previous network meta-analyses have been published in the field of HepatoPancreatoBiliary (HPB) surgery, and it is important to evaluate this new method

of meta-analysis in HPB surgery because it is a valuable research tool with important advantages, as discussed in Chapter 3. The topics identified for systematic reviews, pairwise meta-analyses, and network meta-analyses in this thesis are shown in Table 1.4.

Table 1.4: Topics identified for systematic review in this thesis.

Theme	Aim	Comparison
Timing of liver resections	Identify the best timing for liver resections in patients presenting with synchronous CLM	Combined liver and bowel resection versus sequential resection for synchronous CLM
Liver resection in the presence of hepatic node metastases	Compare survival and disease recurrence in node positive versus node negative disease, assess whether liver resection should be performed in patients with hepatic lymph node metastases, and whether there is a survival benefit from lymphadenectomy	Survival and disease recurrence of lymph node positive versus lymph node negative disease
Decrease blood loss during elective liver resection	Identify the best combination of methods to decrease blood loss during elective liver resection	Assess the comparative benefits and harms of different treatment strategies aiming to decrease blood loss
Reporting the follow-up period in a trial	Investigate whether not reporting the follow-up period in comparative trials of patients with CLM is a potential source of bias	Compare time-to-event outcomes (survival, disease recurrence) of trials reporting versus not reporting period of follow-up
Decrease IR injury during elective liver resection	Identify the best methods to decrease IR injury during elective liver resection	Compare the benefits and harms of different methods aiming to decrease IR injury

Performing the above systematic reviews will benefit, most importantly, the patients suffering with CLM. With the above meta-analyses, the best methods of liver resection will be identified, aiming to decrease the mortality and morbidity related to the operation. The timing of liver resection for patients with synchronous CLM, and whether liver resection is indicated in patients with CLM and hepatic node metastases, will benefit these two important subgroups of patients with CLM. Furthermore, these systematic reviews will provide information to surgeons about the best methods of performing liver resection for CLM, the best timing for resection of synchronous CLM, and indications for liver resections. Identification of new areas of research and possible

sources of bias in comparative trials will benefit the researchers involved in trials comparing treatments for CLM and liver resection. In addition, the above systematic reviews will assist healthcare managers by providing information as to whether special equipment can improve the results of liver resection surgery and decrease the hospital costs. Finally, the review of the literature on such an important topic related to a large number of publications will assist guideline developers in developing guidelines for the management of patients with CLM.

1.4 THESIS HYPOTHESIS AND AIM

Hypothesis:

The hypothesis of the current thesis is that the optimal and effective approach for management of colorectal liver metastases can be identified by using the available published data through the application of an evidence based methodology.

Aim:

Through a series of systematic reviews, pairwise meta-analyses, and network meta-analyses of published data, this thesis aims to identify the best approach to optimal surgical management of CLM in order to provide patients suffering with CLM the best possible care. The above hypothesis will be tested by assessing the quality of the available evidence and by assessing whether further research is necessary and how this should be conducted.

CHAPTER 2

PAIRWISE META-ANALYSIS

2.1 DEFINITION

Meta-analysis is a statistical and analytical technique designed to integrate and summarise the results of multiple independent studies.[128]

2.2 ADVANTAGES AND DISADVANTAGES

There is a vast array of information and diversity of evidence in the medical literature. CLM is an example of a medical condition where many thousands of medical papers have been published on its pathogenesis, diagnosis, treatment, and prognosis. The amount of information in the medical literature has become overwhelming, resulting in a need for review articles which summarise the large volumes of information available and allow conclusions to be drawn. A systematic review has a formal approach to gathering, evaluating, and presenting the medical evidence. A meta-analysis is similar to a systematic review article, with the added step of using formal statistical methods to calculate a summary result or results. Therefore, a meta-analysis has the added advantage of a systematic qualitative and quantitative analysis to support its findings or arguments.

There are many situations where multiple studies may have been published on a medical topic, but due to their small individual size, they may have not been able to demonstrate with statistical significance a difference which does exist between two medical modalities. This is known as a type II error, which occurs when the null hypothesis (H_0: no difference between interventions) is false, but erroneously fails to be rejected. The power of a statistical test is the probability that it correctly rejects the null hypothesis when the null hypothesis is false, and is equal to 1-β, where β is the probability of a Type II error occurring. By combining many studies of small size, a meta-analysis increases the overall sample size of the statistical analysis, and thus increases the power to study effects of interest.[128] Therefore, a meta-analysis has more power than individual studies to identify a true difference that exists between two interventions, especially for outcomes that require larger sample sizes. In addition, a meta-analysis not only has more power to identify statistical difference, but also, increases the precision in estimating the size of the effects of difference

between treatments.[128] As more data is included in a meta-analysis, the precision and accuracy of estimates can be improved, and this, in turn, may increase the statistical power to detect an effect.

Instead of performing large expensive randomised controlled trials (RCTs) to answer important clinical questions, or in situations where an RCT cannot be performed due to practical or ethical concerns, meta-analyses can be an inexpensive alternative and can in this way shape healthcare policies.[128] A well-designed meta-analysis can provide valuable information for clinicians, researchers, managers, and policymakers.[128] Often, meta-analyses may form the initial step of a cost-effectiveness analysis, decision analysis, or grant application. Meta-analyses can be used to design future research, to provide evidence in the regulatory process, and to modify clinical practice.[129]

The role of meta-analytic techniques has been a source of extensive debate amongst epidemiologists. Summarizing large amounts of varied information using a single number is a controversial aspect of meta-analysis.[128] There is a concern that all biases inherent to the individual studies, are brought into the meta-analysis. Critics argue that the effect of meta-analysis is to "reinforce the inherent systematic biases of the studies, produce spurious statistical stability and discourage further research."[130, 131] Another argument against meta-analysis is that it may include and compare studies of different methodology and with different inclusion criteria for participants, therefore comparing different groups of participants with different characteristics. If studies are clinically diverse then a meta-analysis may be meaningless, and genuine differences in effects may be obscured.

Compared with single RCTs, meta-analysis not only improves the power to detect differences between treatments, but also facilitates the examination of the extent to which there are important differences in treatment effects across RCTs.[132] This between-study variability in a group of studies is frequently called heterogeneity. With a meta-analysis, inconsistency or variation in results across studies can be identified, quantified, and analysed. Identifying heterogeneity between studies raises more questions and promotes further research to identify the source of heterogeneity between studies. On the other hand, large, unexplained heterogeneity may reduce a reader's confidence in estimates of treatment effects of a meta-analysis.[132]

Multiple studies may have been published on a medical topic with conflicting results. In these situations, meta-analyses can help resolve medical controversies or uncertainties caused by conflicting studies by pooling all the results of the individual studies and produce a summary result. Pooling the results of conflicting studies in order to produce a summary result can be done only in the absence of clinical or methodological heterogeneity. If there are conflicting results because of clinical or methodological heterogeneity, it is usually inappropriate to perform a meta-analysis.

Distinction should be made between "synthetic" meta-analysis, in which a single summary is reported while heterogeneity is ignored, and "comparative" meta-analysis, in which heterogeneity is taken into account and attempts are made to explain it.[133] The latter serves as an aid in critical comparison between studies, and there seems to be general agreement that the "comparative" approach has a place in medical literature and may complement qualitative reviews.[130, 134] Proponents of meta-analysis argue that statistical quantification and pooling of results from many studies provide an excellent tool for identifying reasons for variability and inconsistency, and that the finding of heterogeneity sets the stage for further research on a given topic.[135]

Moreover, a meta-analysis allows the evaluation of the effects in subsets of patients.[128] If there is a difference between groups of participants in a meta-analysis (e.g. cirrhotic vs non-cirrhotic livers), which may act as a confounding factor or moderator, a meta-analysis allows sensitivity analysis to be performed on a specific subset of patients. Also, moderators can be included in a meta-analysis to explain variation between studies. Metaregression is a useful tool used in meta-analysis to identify confounding factors or moderators and examine their impact on study effect size using regression-based techniques. Furthermore, publication bias occurs because studies with a statistically significant outcome are more likely to be published that those that don't. There is concern that these studies are more likely to be included in a meta-analysis. Nevertheless, with a meta-analysis, the presence of publication bias can be identified and investigated with the help of funnel plots.

A meta-analysis has the potential of generating new hypotheses for future studies, and overall promotes and helps guide further research. On the other hand, a meta-

analysis has the ability to determine if new studies are needed to further investigate a specific clinical question.[128] For example, if the results of a well-conducted meta-analysis are statistically significant with no heterogeneity between numerous high quality RCTs, a valid argument can be made that no further trials are required attempting to answer the same clinical question. First, it would be unethical to perform another trial on patients or animals when the research question has already been answered confidently, and second, with the limited funding available to research, the funding will be better spent on trials attempting to solve new unanswered research questions.

Many researchers believe that meta-analyses should be conducted only on RCTs. Very often in surgery, due to the nature of the specialty, there are no RCTs on a clinical subject, and meta-analyses are performed based on non-randomised studies. There is an obvious disadvantage in using non-randomised studies due to their inherent biases which are transferred into the meta-analysis. Nevertheless, there is an argument to be made in performing meta-analyses on non-randomised studies when RCTs are not available. Deeks *et al.* evaluated non-randomised intervention studies by using resampling techniques (generated non-randomised studies from two large multicentre RCTs and selectively resampled trial participants according to allocated treatment, centre and period), and have found that "results of randomised and nonrandomised studies sometimes, but not always, differ and that both similarities and differences may often be explicable by other confounding factors".[136] They also argued that non-randomised studies should be undertaken when randomization is "unfeasible or unethical."[136] Meta-analysis of non-randomised studies is useful in the absence of RCTs as well as to guide further researchers toward properly informed randomisation, if possible, in future studies.

2.3 METHODS

In this section, an overview of the methods followed in the meta-analyses included in this thesis is described. The first step was to decide the clinical question or clinical subject that needed to be systematically reviewed, and the research hypothesis was defined.

2.3.1 Search strategy

The second step was to perform a literature search to identify the studies for inclusion in the meta-analyses. A comprehensive literature search was performed using a combination of free-text terms and controlled vocabulary when applicable of the following electronic databases: MEDLINE, EMBASE, Science Citation Index Expanded, and Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. The specific search strategies for the meta-analyses conducted are described in more detail in the individual sections of this thesis. The “related articles” function from PubMed was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed. The references of the identified trials were also searched to identify additional trials for inclusion.

2.3.2 Studies for inclusion

Two authors independently identified studies for inclusion by screening titles and abstracts. The two authors performing this step for each meta-analysis performed are named in the individual sections of this thesis. Further selection was based on full text. In order to select the studies for inclusion in the meta-analysis, clear inclusion and exclusion criteria were used. It was important to select carefully, clearly define, and strictly follow these criteria, in order to include studies in the meta-analysis of the same or similar design and methodology; otherwise the results of the meta-analysis would not have been valid if trials of different methodology and different groups of patients were compared. Similarly, the outcomes to be evaluated were

clearly defined to allow the extraction of the necessary data from the included studies and to perform the appropriate statistics.

2.3.3 Data extraction

Two reviewers independently extracted the data from each included study using a standardized custom-designed data extraction form. The two authors extracting the data for each meta-analysis are named in the individual sections of this thesis. The data extracted from the studies included details of the study (e.g. first author, year of publication, country of study), study population characteristics including age and gender, study design, inclusion and exclusion criteria used in individual studies, matching criteria, number of individuals entering the study, follow-up period, lost to follow-up, perioperative outcomes (e.g. mortality, morbidity, operating time, operative blood loss, length of hospital stay). Additional information was extracted by each study depending on the outcomes investigated by the meta-analysis. There should be 100% agreement among the two reviewers in the data extraction. If a 100% agreement was not achieved, any discrepancies were resolved through discussion, and if there was still a disagreement between authors, the final decision was taken by the most senior co-author.

2.3.4 Data analysis

Pairwise meta-analysis was conducted using Review Manager (RevMan) Versions 5.1 and 5.2.[137, 138] The meta-analyses were performed according to the recommendations from Preferred Reporting Items for systematic Reviews and Meta-Analyses (PRISMA) statement.[139] The unit of analysis was the individual patient in all the reviews. All the analyses were performed by an intention-to-treat analysis.

Statistical analysis of dichotomous or binary variables was performed using the Odds Ratio (OR) as the summary statistic reported with 95% Confidence Intervals (CI).[140] OR represents the odds of an event occurring in the intervention group compared to the control group. An OR of less than one favours the intervention group for an adverse

event and the point estimate of the OR was considered to be statistically significant at the $P < 0.05$ level if the 95% confidence interval did not include the value one. Note that zero cells (i.e. no events in one group) cause problems with computation of estimates and standard errors. The RevMan software automatically adds 0.5 to each cell of the 2×2 table for any such study.[141] If there were no events for both the intervention and control groups, the study was discarded from the meta-analysis for that particular outcome.

Continuous variables were analysed using the mean difference (MD) as the summary statistic reported with 95% CI.[140] MDs summarised the differences between the intervention and control groups with respect to continuous variables, accounting for sample size. The point estimate of the MD was considered to be statistically significant at the $P < 0.05$ level if the 95% confidence interval did not include the value zero. For continuous outcomes, if the data were likely to be normally distributed, the median was used for the analysis when the mean was not available. If standard deviation (SD) was not available from a study, the SD was imputed from the standard error (SE), P values, confidence intervals (CIs), or interquartile range, according to guidance given in the Cochrane Handbook for Systematic Reviews of Intervention.[142] If it was not possible to calculate the SD from the SE, P value, CIs, or interquartile range, the SD was imputed using the largest SD in other trials for that outcome.

The hazard ratio (HR) was used for time-to-event outcomes, e.g. to compare overall survival and disease free survival between the intervention and control groups, and was reported with 95% Confidence Intervals (CI). If the HR with 95 % CI was not reported in the publications, the values were calculated from other information and the Kaplan–Meier curve using methods described by Parmar *et al.*[143] The point estimate of the HR was considered to be statistically significant at the $P < 0.05$ level if the 95% confidence interval did not include the value one.

The Mantel–Haenszel (MH) method and the DerSimonian Laird method were used to combine the binary outcomes, and the generic inverse variance method was used to combine the time-to event outcomes. The random-effects model[140] and the fixed-effect model[144] were used for the meta-analyses. Where there was no difference between the results of random-effects and fixed-effect models that would change

interpretation of the results, the results of the fixed-effect model were reported; otherwise, both the results were reported.

The fixed-effect model assumes that all included studies investigate the same population, use identical methods, use the same variable and outcome definitions, and should produce identical results.[141] Any differences noted between the studies, is sampling variation according to the fixed-effect model. The Peto and Mantel-Haenszel (MH) statistical methods are both based on a fixed effects model. With the fixed-effect model larger studies have more weight because the inverse of a study's estimate variance is used as study weight.

The random-effects model takes into consideration both between-study and within-study variability, and it assumes that the different studies are estimating different, yet related, intervention effects.[140, 141] The random-effects model is based on the inverse-variance approach, making an adjustment to the study weights according to the extent of heterogeneity between the varying intervention effects.[141] The amount of heterogeneity, and hence the adjustment, can be estimated from the intervention effects and standard errors of the studies included in the meta-analysis.[141] The DerSimonian Laird statistic is based on a random effects model.[140]

The random-effects and the fixed-effect models give identical results if there is no heterogeneity between the studies, whereas in the presence of heterogeneity, the CI of the meta-analysed measure of effect will be wider if the random-effects model is used rather than the fixed-effect model.[141] Therefore, the random-effects model is thought to provide a more conservative value because it assumes that there is a variation between studies due to heterogeneity, and generates a wider CI.[140, 145] The random-effects model is preferable by some researchers when meta-analytical techniques are undertaken in surgical research for a given surgical technique in which each study centre has differing patient selection criteria and patient risk profiles.

Heterogeneity between the included studies was crudely assessed by examining the forest plot. If confidence intervals for the results of individual studies (depicted graphically using horizontal lines) had no overlap or poor overlap, this indicated the presence of statistical heterogeneity. In addition, if the effect estimates of the individual studies lied on either side of the line of no effect (Figure 2.1), then the heterogeneity

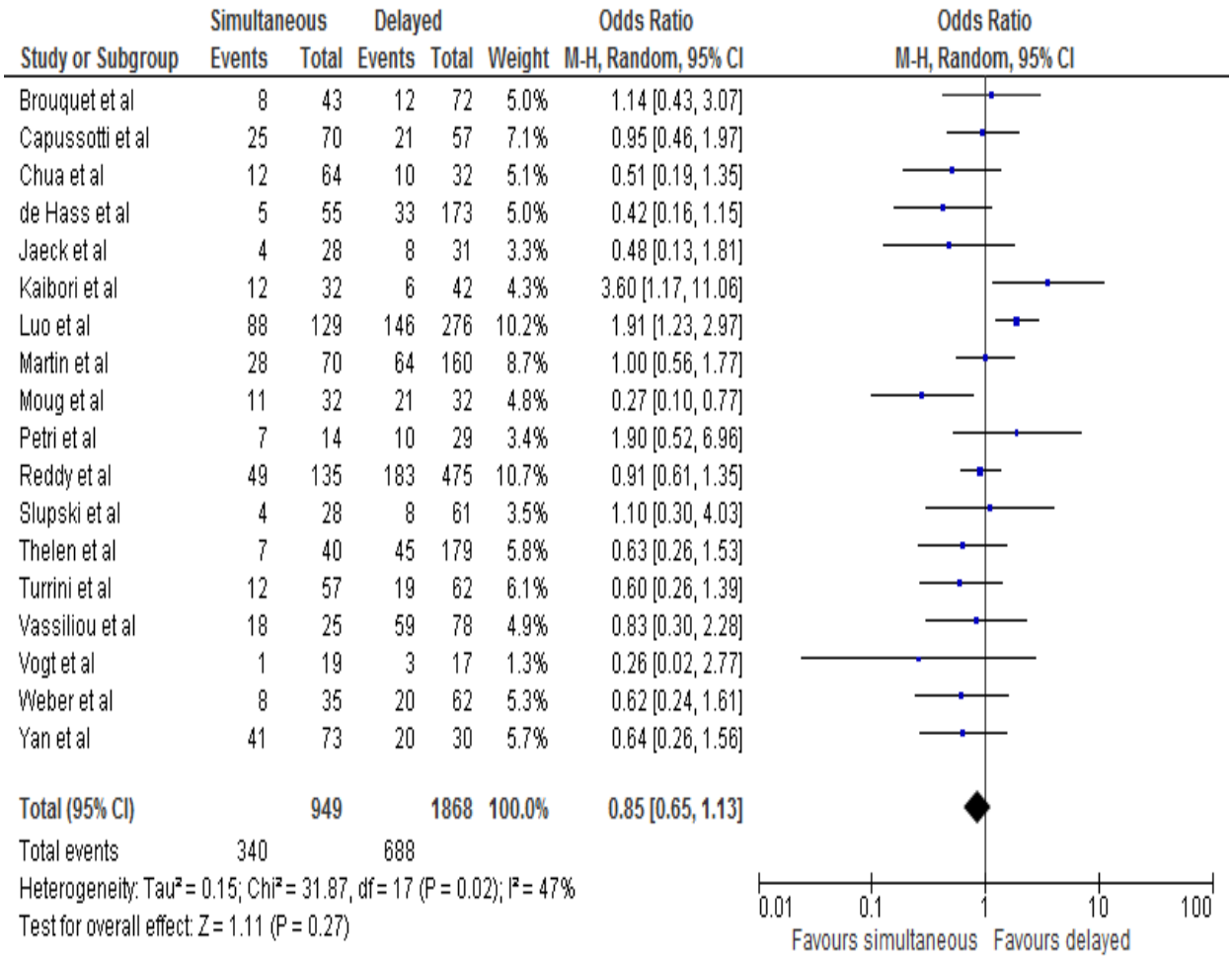
was in the direction of the effect which meant that the beneficial or harmful effect of the intervention was not consistent across studies. On the other hand, if all the point effect estimates of the individual studies lied on the same side but at different distances from the line of no effect, then the heterogeneity was in the magnitude of the effect which meant that all the studies consistently reported that the intervention was beneficial or harmful but there was variation in how beneficial or harmful the intervention was.

Moreover, heterogeneity was assessed with the chi-squared (X^2 or Chi^2) test, which was included in the forest plots with its P value. Figure 2.1 shows an example of a forest plot. Heterogeneity between studies was suggested if the P value was low or the chi-squared was large. Because the chi-squared test has low power when studies have small sample size or are few in number, heterogeneity among the individual studies was considered to be statistically significant at the more conservative value of $P < 0.10$ level.[141]

The effect of heterogeneity was also quantified by means of I-square (I^2), where the higher the I-square value, the higher was the risk for heterogeneity between studies.[142] I-square describes the percentage of total variation across studies that is due to heterogeneity rather than chance, and it can be calculated using the formula $I^2=100\%\times(Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom.[146] A rough guide to the interpretation of I-square value is as follows:[142]

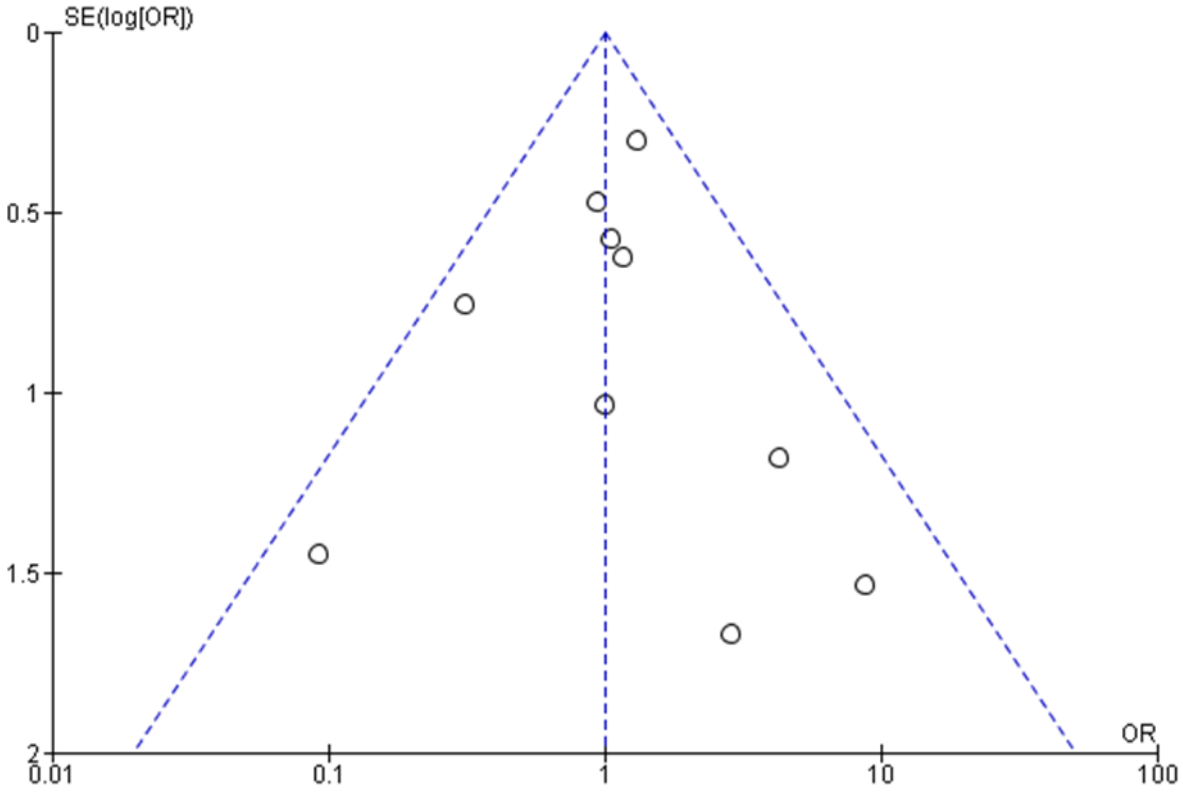
- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Figure 2.1: Forest plot for a binary outcome. Each study represented by a line. The left-hand column lists the surnames of the first authors of the studies included in the analysis in alphabetical order from the top downwards. The middle columns provide the summary data entered for each study, which in this example, show the number of events and the total number of patients in each group separately. Also, it provides the effect measure with 95% CI for each study, the method, and the model used to perform the meta-analysis. In this example, the effect measure is the odds ratio (OR), the statistical method used is the Mantel-Haenszel (MH) method, and the model used is the random-effects model. The right-hand column is a plot of the measure of effect (in this case OR) for each of these studies. The mid-point of the box represents the point effect estimate, that is, the mean effect estimate for each study, and the horizontal lines represent the 95% CI. The area of the square is proportional to the study's weight in the meta-analysis. The vertical line represents no effect. For a bad event, as in this example, the left of the vertical line favours the experimental or intervention group, and the right of the vertical line favours the control group. If the confidence intervals for individual studies overlap with this line, it demonstrates that there is no significant difference between the two groups for this outcome. The diamond below the studies represents the overall meta-analysed measure of effect, the width of which indicates the 95% CI for the overall effect estimate. If the points of the diamond overlap the line of no effect, the overall meta-analysed result shows that there is no significant difference between the two groups for this outcome. Assessment of heterogeneity is demonstrated in the values of I-square and chi-squared with its P value.



Three further strategies were used to quantitatively assess heterogeneity. First, sensitivity analyses were undertaken using subgroups, e.g. studies of higher quality, more recent studies, whether chemotherapy was used in studies etc. Second, data were analysed using both random-effects and fixed-effect models. Third, graphical exploration with funnel plots was used to evaluate publication bias.[145, 147] Figure 2.2 shows an example of a funnel plot.

Figure 2.2: Funnel plot for the same binary outcome as in Figure 2.1. A funnel plot is a scatterplot of the treatment effect (represented as OR estimated from individual studies) plotted on the horizontal axis, against a measure of study size (represented as the standard error of the estimate) shown on the vertical axis (SE[logOR]). In the absence of publication bias, it assumes that the largest studies will be plotted near the average, and smaller studies will be spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Deviation from this shape can indicate publication bias. The blue lines represent the overall effect estimate and the 95% CI.



2.3.5 Other details

The bias, quality of evidence of included studies, inclusion and exclusion criteria for each review, and the requirement for further trials are mentioned in detail in the relevant chapters.

CHAPTER 3

NETWORK META-ANALYSIS

3.1 DEFINITION

A network meta-analysis uses meta-analytical techniques to compare multiple treatments which have been used and compared for the same disease and outcomes in different head-to-head comparisons.

3.2 ADVANTAGES AND DISADVANTAGES

On one medical topic, there may have been hundreds of studies comparing surgical interventions for the same outcomes, e.g. trials comparing different methods aiming to decrease blood loss during liver resections, or interventions aiming to decrease IR injury during liver resection. Dozens of pairwise meta-analyses may have been carried out to bring together and analyse the results of all the individual interventions. But, one of the disadvantages of a pairwise meta-analysis is that it can only compare two treatments at a time, i.e. it only permits comparison of the effects of one intervention versus one comparator, rather than all available surgical treatments simultaneously.

Furthermore, if two treatments have not been compared directly against each other in trials, it is not possible to calculate the relative effects of the two treatments. Yet, for many medical or surgical conditions, there are numerous treatments which have been compared with a no treatment control group, but not with one another.[132] For example, many interventions have been tested aiming to decrease ischaemic reperfusion injury during liver resection for CLM but have not been compared against one another. Sometimes, to overcome these problems, pairwise meta-analyses group together interventions that should not be grouped together due to their different mechanisms of action, in order to be able to perform a pairwise comparison.

Network meta-analysis, is a new method of comparison of different treatments, and is ideal when multiple interventions have been used and compared for the same disease and outcomes in different head-to-head comparisons. An advantage of network meta-analysis over standard pairwise meta-analysis is that it combines direct evidence within trials and indirect evidence across trials facilitating indirect comparisons of multiple interventions that have not been studied in a head-to-head fashion.[132, 148] Therefore, a

network meta-analysis provides estimates of effect sizes for all possible pairwise comparisons that may or may not have been evaluated directly against each other, and allows inferences into the comparative effectiveness of different treatments to be assessed even if they have not been compared directly in individual RCTs.

An example of a direct comparison between two interventions is shown in Figure 3.1, in this case A and B. A standard pairwise meta-analysis could be performed on trials comparing treatments A and B. An example of a simple indirect comparison for B and C is shown in Figure 3.2, when no trials are available comparing treatments B and C. An example of a simple closed loop is shown in Figure 3.3, where interventions A, B, and C, have all been compared against each other at some point in previous trials. A network meta-analysis could be performed to compare the treatments in examples 3.2 and 3.3 by combining direct evidence within trials and indirect evidence across trials. An example of a network meta-analysis plot (or network plot) is shown in Figure 3.4, with the comparisons between treatments.

Figure 3.1: Example of a direct comparison. A and B are examples of two interventions and the continuous arrow represents a direct comparison between the two interventions.

Figure 3.2: Example of a simple indirect comparison. A, B, and C, are examples of three interventions. The continuous arrows represent a direct comparison between the interventions in previous trials. The intermittent arrow represents a simple indirect comparison for B and C, when no trials are available comparing treatments B and C.

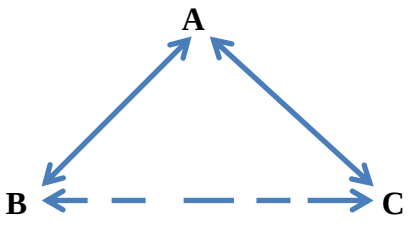


Figure 3.3: Example of a simple closed loop. A, B, and C are examples of interventions. The continuous arrows represent a direct comparison between the interventions. In this example all interventions have been compared against each other at some point in previous trials.

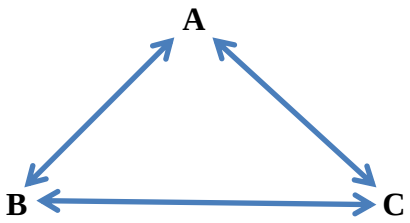
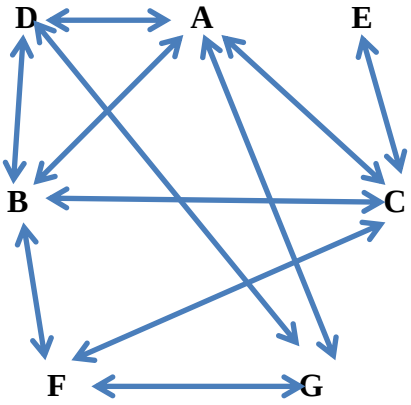


Figure 3.4: Example of a network plot. A to G are examples of interventions. The continuous arrows represent a direct comparison between the interventions in previous trials.



Visualising the geometry of a network plot permits the reader to understand the larger picture and see what is compared with what.[149] The presence of direct evidence increases confidence in the estimates of interest, and the extent to which the treatments are connected in the network is an important determinant in the quality of the evidence.[132, 149] For example, a star network plot (Figure 3.5) occurs when different interventions have only been compared with a single common comparator (e.g., no intervention or placebo), and only allows for indirect comparison between interventions,

which reduces confidence in effects, particularly if there are a limited number of trials, patients, and events.[132, 150] On the other hand, in a connected network plot all interventions have been compared against each other. In a complex network plot (Figure 3.6), which is the most common, data is available using a mixture of direct and indirect evidence. An example of a star network plot is shown in Figure 3.5. Figure 3.6 shows an example of a complex network plot.

Figure 3.5: An example of a star network plot involving interventions aiming to reduce hepatic IR injury during liver surgery taken from Chapter 7. Circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison, also represented by the numbers.

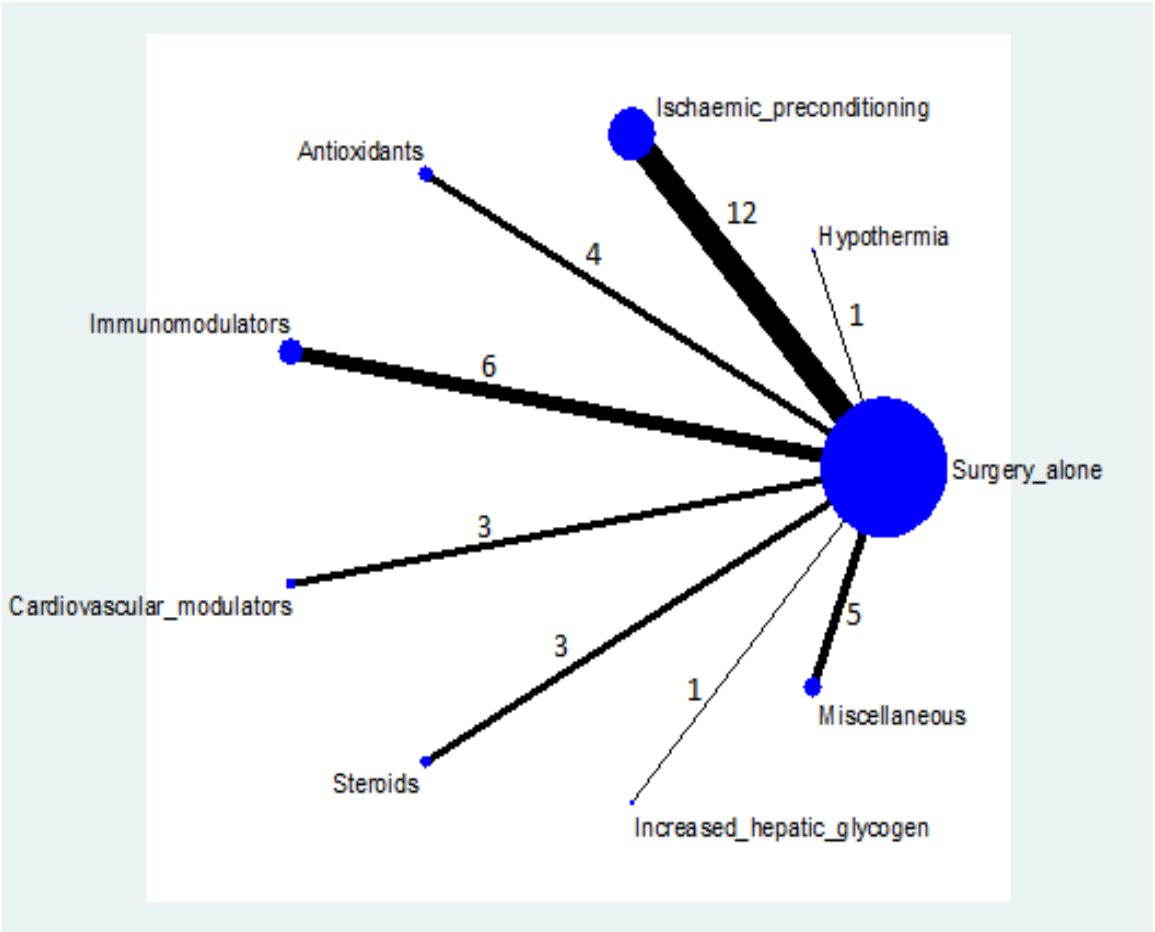
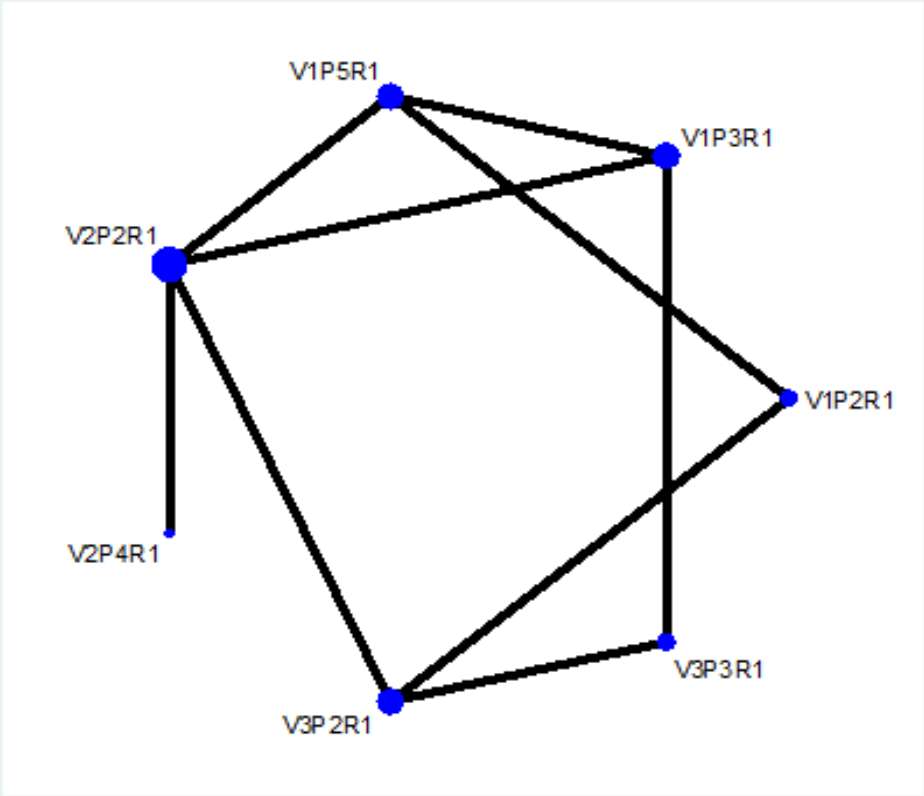


Figure 3.6: An example of a complex network plot involving treatment strategies during liver resection aiming to reduce blood loss and blood transfusion. The codes of the treatment strategies (e.g. V1P4R1) will be explained in detail in Chapter 6. Circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; .



A network meta-analysis allows us to visualize and interpret a wider picture of the available evidence, and to calculate treatment rankings with probabilities.[132, 148] Also, an advantage of a network meta-analysis compared to large RCTs, is that a very high number of participants is required to show a significant benefit or harm of a treatment for a clinical outcome if all the different interventions have to be compared in a single multiple arm RCT, and RCTs of this magnitude are unlikely to be funded.

By including evidence from both direct and indirect comparisons, a network meta-analysis may increase the precision in estimates of the relative effects of treatments, and it may yield more reliable and definitive results compared to a pairwise meta-analysis.[132, 148] Because network meta-analyses include evidence from both direct and indirect comparisons, power may be better than in standard pairwise meta-analyses that include only direct evidence. Nevertheless, where direct and indirect evidence exists in a network meta-analysis, it has to be ensured that the findings are sufficiently consistent between direct and indirect comparisons. In the face of large incoherence between direct and indirect evidence in a particular comparison the GRADE working group suggested to focus attention on the direct or indirect estimate warranting greater confidence, rather than the network meta-analysis estimate, as the best estimate of effect. Or, alternatively, to focus on the network meta-analysis estimate but rate down the quality of that estimate due to incoherence.[151]

An important assumption made in network meta-analyses in order to allow direct and indirect comparisons, is that all the included trials in the comparisons are sufficiently homogeneous, especially regarding essential features, for example, patient characteristics, definitions and measurements of outcomes, period of follow-up, and risk of bias in the studies.[132] It is important to avoid broad inclusion criteria for the trials, in order to avoid heterogeneity. For example, in this thesis there was a strict inclusion criterion for studies to be RCTs to be included in the network meta-analysis in order to minimise the inherent biases and differences in methodology between the included studies. Nevertheless, RCTs are difficult to carry out in the field of surgery as the speciality is largely craft based and dependent on operator skills.

The different RCTs included in a network meta-analysis are at different risk of bias. If significant clinical variability or statistical heterogeneity is present between trials, subgroup analysis or meta-regression can be performed to attempt to explain the heterogeneity. Due to the greater number of RCTs in network meta-analyses, there are more opportunities for subgroup analysis, as long as all the trials are still connected in the network plot of the subgroup analysis.

3.3 METHODS

The methods for literature search, identification of studies for inclusion, and data extraction used for network meta-analysis are similar to those used for pairwise meta-analysis as described in Chapter 2. Sections 2.2.1 (Search strategy), 2.2.2 (Studies for inclusion), and 2.2.3 (Data extraction), are applicable to the methods used for network meta-analysis. There are differences in the data analysis between network and pairwise meta-analyses, and these differences are described next in Section 3.3.1 (Data analysis).

3.3.1 Data analysis

For binary data, based on the number of patients developing the adverse event, a binomial model was used for the analysis and the odds ratio (OR) was calculated. For outcomes where some patients may develop multiple adverse events, the total number of adverse events rather than the number of patients was imputed in the analysis, and a Poisson model was used. An arbitrary constant of 1 was added to the denominator and 0.5 to the numerator for trials with zero-event outcomes. For continuous outcomes the mean difference (MD) was calculated, and if the data were likely to be normally distributed, the median was used for the analysis when the mean was not available.

For each outcome of interest, Stata/IC 11 (StataCorp LP) was used to draw a network plot of all the interventions assessed for that specific outcome. Circles represented the intervention as a node in the network, lines represented direct comparisons using RCTs, and thickness of lines represented the number of RCTs included in each comparison. Any interventions that were not connected to the other interventions through the network plot were excluded from the analysis of that outcome. Therefore, the trials reporting on those interventions that were not connected to the network plot were also excluded from the network meta-analysis of that outcome.

A Bayesian network meta-analysis was conducted using the Markov chain Monte Carlo method in WinBUGS 1.4. A treatment contrast means a pairwise comparison between two treatments expressed as OR for binary outcomes and MD for continuous outcomes. The treatment contrast for any two interventions was modelled as a function of

comparisons between each individual intervention and an arbitrarily selected reference group.[152] Choice of the reference group was based on ease of interpretation, with placebo or standard treatment usually taken as the reference group (or Treatment 1). In larger networks, Treatment 1 was chosen to be the treatment that is in the "centre" of the network, i.e. the treatment that has been trialled against the highest number of other treatments.

The network analysis was performed as per the guidance from The National Institute for Health and Clinical Excellence (NICE) Decision Support Unit (DSU) documents.[153] The influence of study design and other potential sources of heterogeneity on effect estimates were assessed by metaregression. Details of the codes used and the raw data included in WinBUGS 1.4 are shown in sections 3.3 and 3.4. The codes allow handling of trials with multiple arms to be dealt in the same way as two-arm trials and take into account the correlation between effect sizes introduced by multi-arm studies. One can enter the data from all the arms in a trial as number of events and the number of people exposed to the event for binary outcomes or the mean and standard error for continuous outcomes.

The posterior probabilities (effect estimates or values) of the treatment contrast (i.e., log odds ratio or mean difference) may vary depending upon the initial values to start the simulations in WinBUGS. In order to control the random error due to the choice of initial values, the network meta-analysis was performed for three different initial values (priors) as per the guidance from the NICE DSU documents.[153] If the results from three different priors are similar (convergence), then the results are reliable. It was important to discard the results of the initial simulations as they can be significantly affected by the choice of the priors, and only the results of the simulations obtained after the convergence were included. The discarding of the initial simulations is called 'burn in'. The models for all binary and continuous outcomes were run for 10,000 simulations (i.e. the number of times that the values are calculated by the software, the values being sampled from a distribution based on the data from the studies) for 'burn in' for three different chains (a set of initial values). The models were run for another 20,000 simulations to obtain the effect estimates. The exceptions to this were when the model did not converge for a variable, and further simulations were run until they converged. The effect estimates from the results of all the three chains (different initial values) were obtained. The results in the three different chains were examined to ensure that they

were similar in order to control for random error due to the choice of priors. This was done in addition to the visual inspection of convergence obtained after simulations in the burn in.

Three different models were run for each outcome: fixed-effect model, random-effects model, and random-effects inconsistency model. Fixed-effect model assumes that the treatment effect is the same across studies. The random-effects consistency model assumes that the treatment effect is distributed normally across the studies but assumes that the transitivity assumption is satisfied (i.e., the population studied, the definition of outcomes, and the methods used were similar across studies and that there is consistency between the direct comparison and indirect comparison). The between-study random-effects was considered to be the same across treatment comparisons. A random-effects inconsistency model does not assume transitivity assumption. If the inconsistency model resulted in a better model fit than the consistency model, the results of the network meta-analysis can be unreliable and so should be interpreted with extreme caution. If there was evidence of inconsistency, we planned to identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit network meta-analysis to a more compatible subset of trials.

Heterogeneity may be characterised as between-trial variation within treatment contrasts, and inconsistency as variation between contrasts. The residual deviance and DIC were used for assessing between study heterogeneity as per the guidance from the NICE DSU Technical Support Documents.[153, 154] The between trial SD was also calculated and reported if random-effects model was used. The model fit was assessed by deviance residuals and Deviance Information Criteria (DIC) according to NICE DSU guidelines.[153] The treatment contrasts (OR for binary outcomes and MD for continuous outcomes) of the different treatments in relation to the reference treatment, the deviance residuals, number of effective parameters, and DIC for fixed-effect model and random-effects model were reported for each outcome. Also, the parameters used to assess the model fit (i.e. deviance residuals, number of effective parameters, and DIC) for the inconsistency model were reported. The choice of the model between fixed-effect model and random-effects model was based on the model fit. A lower DIC indicates a better model fit, but a difference of three or five in the DIC is not generally considered important.[154] The simpler model, which is the fixed-effect model was used if the DIC

were similar between the fixed-effect model and random-effects model. The random-effects model was used if it resulted in a better model fit as indicated by a DIC lower than that of fixed-effect model by at least three.

Network meta-analyses may be more prone to the risk of random errors than direct comparisons.[155] Accordingly, a greater sample size is required in indirect comparisons than direct comparisons.[156] The power and precision in indirect comparisons depends upon various factors such as the number of participants included under each comparison and the heterogeneity between the trials.[156] If there was no heterogeneity across the trials, the sample size in indirect comparisons would be equivalent to the sample size in direct comparisons. The effective indirect sample size can be calculated using the number of participants included in each direct comparison.[156] For example, a sample size of 2500 participants in the direct comparison A versus C (n_{AC}) and a sample size of 7500 participants in the direct comparison B versus C (n_{BC}) results in an effective indirect sample size of 1876 participants. However, in the presence of heterogeneity within the comparisons, the sample size required is higher. In the above scenario, for an I^2 statistic for each of the comparisons A versus C (I_{AC}^2) and B versus C (I_{BC}^2) of 25%, the effective indirect sample size is 1407 participants. For an I^2 statistic for each of the comparisons A versus C and B versus C of 50%, the effective indirect sample size is 938 participants.[156] The effective indirect sample size can be calculated using the following generic formula:[156]

$((n_{AC} \text{ x } (1 - I_{AC}^2)) \text{ x } (n_{BC} \text{ x } (1\text{-}I_{BC}^2))/((n_{AC} \text{ x } (1 - I_{AC}^2)) + (n_{BC} \text{ x } (1\text{-}I_{BC}^2))$.

The effect estimates of the treatment and the 95% credible intervals (CrI, similar to the 95% CI in a frequentist method of meta-analysis) were calculated using the formulae for calculating the effect estimates in indirect comparisons:[157]

$\ln(OR_{AC}) = \ln(OR_{AB}) - \ln(OR_{CB})$ and $\text{Var}(\ln OR_{AC}) = \text{Var}(\ln OR_{AB}) + \text{Var}(\ln OR_{CB})$

where ln indicates natural logarithm; OR indicates odds ratio; Var indicates variance; and A, B, and C are three different treatments.

The effect estimates and associated 95% CrI for each pairwise comparison were reported in a table. Also, the probability that each intervention ranks at one of the

possible positions was estimated. The probability that a treatment ranks as the best treatment for each outcome of interest, was presented in graphs. It should be noted that a less than 90% (<90%) probability that the treatment is the best treatment is unreliable.[158] The cumulative probability of the treatment ranks (i.e. the probability that the treatment is within the top two, the probability that the treatment is within the top three, etc.) was also presented in graphs. In addition, the probability that each treatment is best for each of the different outcomes (rankogram) was plotted, which is generally considered more informative.[158, 159]

3.4 WINBUGS CODES

Below are the codes used in WinBUGS 1.4 for the network meta-analyses of binary and continuous outcomes. The codes were taken from the NICE DSU website and they have been previously validated by NICE DSU. The codes used are for the fixed-effect model, random-effects consistency model, and random-effects inconsistency model. The codes used for metaregression are also included.

3.4.1 Binary outcome - fixed-effect model

```
# Binomial likelihood, logit link
# Fixed effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor
logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
# ranking on relative scale
```

```
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th
best
}
} # *** PROGRAM ENDS
```

3.4.2 Binary outcome - random-effects consistency model

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
```

```
# adjustment for multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th
best
}
} # *** PROGRAM ENDS
```

3.4.3 Binary outcome - random-effects inconsistency model

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
delta[i,1]<-0 # treatment effect is zero in control arm
mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
```

```
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
for (c in 1:(nt-1)) { # priors for all mean treatment effects
for (k in (c+1):nt) { d[c,k] ~ dnorm(0,.0001) }
}
sd ~ dunif(0,5) # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var # between-trial precision
} # *** PROGRAM ENDS
```

3.4.4 Continuous outcome - fixed-effect model

```
# Normal likelihood, identity link
# Fixed effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
# model for linear predictor
theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
```

```
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th
best
}
} # *** PROGRAM ENDS
```

3.4.5 Continuous outcome - random-effects consistency model

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
```

```
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th
best
}
} # *** PROGRAM ENDS
```

3.4.6 Continuous outcome - random-effects inconsistency model

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
for (c in 1:(nt-1)) { # priors for all mean treatment effects
for (k in (c+1):nt) { d[c,k] ~ dnorm(0,.0001) }
}
sd ~ dunif(0,5) # vague prior for between-trial standard deviation
tau <- pow(sd,-2) # between-trial precision
} # *** PROGRAM ENDS
```

3.4.7 Metaregression binary outcome – fixed-effect model

```
# Binomial likelihood, logit link
# Fixed effects model with continuous covariate
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor, covariate effect relative to treat in arm 1
logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] + (beta[t[i,k]]-beta[t[i,1]]) * (x[i]-mx)
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
beta[1] <- 0 # covariate effect is zero for reference treatment
for (k in 2:nt){ # LOOP THROUGH TREATMENTS
d[k] ~ dnorm(0,.0001) # vague priors for treatment effects
beta[k] <- B # common covariate effect
}
B ~ dnorm(0,.0001) # vague prior for covariate effect
} # *** PROGRAM ENDS
```

3.4.8 Metaregression binary outcome – random-effects consistency model

```
# Binomial likelihood, logit link, continuous covariate
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
```

```
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor, covariate effect relative to treat in arm 1 (centring)
logit(p[i,k]) <- mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]]) * (x[i]-mx)
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
for (k in 2:na[i]) { # LOOP THROUGH ARMS
delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with multi-arm
trial correction)
taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with multi-arm trial
correction)
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
beta[1] <- 0 # covariate effect is zero for reference treatment
for (k in 2:nt){ # LOOP THROUGH TREATMENTS
d[k] ~ dnorm(0,.0001) # vague priors for treatment effects
beta[k] <- B # common covariate effect
}
B ~ dnorm(0,.0001) # vague prior for covariate effect
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
} # *** PROGRAM ENDS
```

3.4.9 Metaregression continuous outcome – random-effects consistency model

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ #   LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2)   # calculate variances
prec[i,k] <- 1/var[i,k]      # set precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
theta[i,k] <- mu[i] + delta[i,k]+ (beta[t[i,k]]-beta[t[i,1]]) * (x[i]-mx) # model for linear
predictor
#Deviance contribution
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
}
#  summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
```

```
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
beta[1] <- 0 # covariate effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)
beta[k] <- B[k] # exchangeable covariate effect
B[k] ~ dnorm(0,.0001) # vague prior for covariate effect
}
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# treatment effect when covariate = z[j] (un-centring treatment effects)
for (k in 1:nt){
for (j in 1:nz) { dz[j,k] <- d[k] - (beta[k]-beta[1])*(mx-z[j]) }
}
# pairwise ORs and LORs for all possible pairwise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
MeanDifference[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th
best
}
} # *** PROGRAM ENDS
```

3.5 RAW DATA

Below are examples of how the binary and continuous data were inserted into the WinBUGS codes for analysis.

3.5.1 Binary outcomes

```
# ns= number of studies; nt=number of treatments
list(ns=7, nt=7)
r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] t[,1] t[,2] t[,3] na[] #study
1.5 37 0.5 38 NA NA 4 6 NA 2 #Petrowsky
2.5 26 0.5 26 0.5 26 2 3 4 3 #Lesurtel
0.5 27 0.5 25 NA NA 1 3 NA 2 #Lupo
0.5 42 0.5 42 NA NA 4 5 NA 2 #Smyrniotis
1 63 1 63 NA NA 1 6 NA 2 #Capussotti
2.5 21 0.5 21 NA NA 6 7 NA 2 #Doklestic
0.5 26 0.5 26 NA NA 2 7 NA 2 #Park
END
```

Footnotes: # ns= number of studies; nt=number of treatments; t[,1] indicates control and t[,2] indicates intervention. In a three-arm trial, t[,3] indicates the second intervention. r[,1] indicates the number with events in the control group; n[,1] indicates the total number of people in the control group. r[,2], n[,2], r[,3], and n[,3] indicate the corresponding numbers for intervention and second intervention. In two-arm trials, r[,3] and n[,3] will be entered as 'NA' to indicate empty cells. If no three-arm trials were included under the outcome, the entire columns r[,3] and n[,3] were not included. na[] indicates the number of arms in the trial. Study indicates the study name and is for reference only.

3.5.2 Continuous outcomes

```
list(ns=6, nt=7)
t[,1] t[,2] t[,3] y[,1] y[,2] y[,3] se[,1] se[,2] se[,3] na[] # study
4 6 NA 14.7 12.7 NA 1.6 1.4 NA 2 # Petrowsky
2 3 4 9 9 9 1.6 1.6 1.6 3 # Lesurtel SE imputed
4 5 NA 10 11 NA 1.6 1.6 NA 2 # Smyrniotis SE imputed
1 6 NA 8.6 8.9 NA 0.4 0.6 NA 2 # Capussotti
6 7 NA 10 8.5 NA 1.6 1.6 NA 2 # Doklestic SE imputed
2 7 NA 19.3 15.8 NA 1.4 0.9 NA 2 # Park
END
```

Footnotes: # ns= number of studies; nt=number of treatments; t[,1] indicates control and t[,2] indicates intervention. In a three-arm trial, t[,3] indicates the second intervention. y[,1] indicates the mean in the control group; se[,1] indicates the standard error in the control group. y[,2], se[,2], y[,3], and se[,3] indicate the corresponding numbers for intervention and second intervention. In two-arm trials, y[,3] and se[,3] will be entered as 'NA' to indicate empty cells. If no three-arm trials were included under the outcome, the entire columns r[,3] and n[,3] were not included. na[] indicates the number of arms in the trial. Study indicates the study name and is for reference only.

CHAPTER 4

PAIRWISE META-ANALYSIS COMPARING COMBINED VERSUS SEQUENTIAL RESECTION FOR SYNCHRONOUS COLORECTAL LIVER METASTASES

4.1 INTRODUCTION

In some people with colorectal cancer, the liver metastases are present at the time of diagnosis of the primary tumour (synchronous metastases) and in others, the liver metastases are identified at a later stage (metachronous metastases). Approximately 15% to 25% of patients with colorectal cancer have detectable liver metastases at the time of presentation (synchronous CLM) and a further 20% to 25% of patients will develop metastases during the course of their disease (metachronous CLM).[10-13] In a French epidemiologic study, the proportion of patients who presented with synchronous CLM was 14.5%, and the 5-year cumulative metachronous liver metastasis rate was 14.5%.[160] In the same study, curative liver resection was performed in 6.3% of synchronous CLM and 16.9% of metachronous liver metastases.[160]

Liver resection is the only curative option for CLM, with five-year survival for patients with CLM who undergo hepatectomy, ranging between 32% and 58%,[19-24, 26, 27, 161] and 10-year overall survival ranging between 22 and 28%.[20-22, 26, 27, 161] The optimal timing of liver resection for resectable synchronous CLM is controversial. Traditionally most surgeons perform a ‘sequential’ (or staged, or delayed) resection, whereby the primary colorectal tumour is resected first followed by a hepatectomy at a later stage.[110] Between the procedures the patients often receive chemotherapy and those with disease progression during chemotherapy are unlikely to be considered for liver resection, thus selecting tumours with better prognosis for liver resection.

More recently, surgeons have started performing ‘combined’ (or simultaneous) resections whereby the primary tumour and liver resection are performed concurrently.[11] Combined resections became more common due to advances in the fields of surgery, anaesthesia, and critical care, allowing surgeons to perform more complex operations safely. The advantages of combined resection over sequential resection is thought to be the decreased operative and anaesthetic risks of one operation versus two operations, with shorter hospital stay and faster recovery allowing patients to commence adjuvant chemotherapy earlier.

Nevertheless, there remain concerns regarding combined resections about both the safety and the long-term oncological effects. This has led surgeons to be cautious and to perform combined resections in a selected group of patients with an easily resectable

primary, limited metastatic disease, and few comorbidities.[111-113] Clinically this usually equates with a right colon resected along with a minor liver resection (<3 segments). There have been previous systematic reviews comparing combined versus sequential resections for synchronous CLM, but they did not report on all the important outcomes of interest and they have missed important studies[112, 162-166] some of which were published after the search date of those systematic reviews.

4.1.1. Aims of this review

The aims of this review were to perform an up-to-date systematic review of the literature to identify the best timing for liver resections in patients presenting with synchronous CLM.

Meta-analytical techniques are used to compare the short and long-term outcomes in patients with synchronous CLM undergoing combined resection (whereby the primary tumour and liver resection are performed concurrently) versus sequential resection (whereby the primary colorectal tumour is resected first followed by liver resection at a later stage).

4.2 METHODS

4.2.1 Search strategy

A comprehensive literature search was performed of the following databases: MEDLINE, EMBASE, and CENTRAL in The Cochrane Library. The following search headings were used: “colorectal liver metastases”, “colorectal hepatic metastases” combined with the Boolean operator ‘AND’ and each of the following terms: “combined resection”, “simultaneous resection”, “synchronous resection”, “sequential resection”, “delayed resection”, and “staged resection”. The “related articles” function from PubMed was used to broaden the search, and all titles were initially scanned and the abstracts of interest were reviewed. The references of the identified trials were also searched to identify additional trials for inclusion. No restrictions were made based on language, publication year, or publication status. The latest date for this search was June 30, 2012.

4.2.2 Inclusion and exclusion criteria

To be included in the analysis, a study had to:

1. Clearly report CLM as synchronous in presentation.
2. Compare combined versus sequential resections in patients with synchronous CLM.
3. Report on at least one of the outcome measures of interest mentioned below in a format that could be used in the meta-analysis.
4. Be either the most recent study or the highest quality study when two or more reports on the same patients were published by the same institution and/or authors.

4.2.3 Data extraction

The following data were independently extracted by two review authors (Constantinos Simillis and Alistair Slesser) from each study using a custom-designed data extraction form: first author, language of publication, country and year(s) of conduct of the study, year of publication, type of study, sample size, the number of subjects undergoing combined and sequential resections, participant characteristics (such as age, sex, underlying disease, comorbidities), inclusion and exclusion criteria used in individual studies, matching criteria, follow-up period, patients lost to follow-up, data for the outcomes of interest mentioned below, and risk of bias. Any discrepancies between the two reviewers were resolved through discussion.

The risk of bias and the quality of the included studies was assessed based on the Newcastle-Ottawa Scale (NOS) with some modifications to match the needs of this study.[167-169] The quality of the studies was evaluated by the same two review authors by examining three factors: patient selection, comparability of the study groups, and assessment of outcome. Table 4.1 shows how the stars were awarded for each study based on the modified NOS.

Table 4.1: Modified Newcastle-Ottawa Scale (NOS) for assessing the quality of the included studies.

Assessment of quality of included studies – Newcastle Ottawa Scale	
Selection (tick one box in each section)	
1. Representativeness of the intervention cohort a) truly representative of the average, elderly, community-dwelling resident ★ b) somewhat representative of the average, elderly, community-dwelling resident ★ c) selected group of patients, e.g. only certain socio-economic groups/areas d) no description of the derivation of the cohort	☐ ☐ ☐ ☐
2. Selection of the non-intervention cohort a) drawn from the same community as the intervention cohort ★ b) drawn from a different source c) no description of the derivation of the non-intervention cohort	☐ ☐ ☐
3. Ascertainment of intervention a) secure record (e.g. health care record) ★ b) structured interview ★ c) written self-report d) other / no description	☐ ☐ ☐ ☐
4. Demonstration that outcome of interest was not present at start of study a) yes ★ b) no	☐ ☐
Comparability (tick one or both boxes, as appropriate)	
1. Comparability of cohorts on the basis of the design or analysis a) study controls for age, sex, BMI/weight, ASA grade, cardiorespiratory disease (any 3 of the 5) ★ b) study controls for any additional factors (number of metastases, distribution of metastases, size of metastases, location of colon cancer, staging of colon cancer) (any 2 of 5) ★	☐ ☐
Outcome (tick one box in each section)	
1. Assessment of outcome a) independent blind assessment ★ b) record linkage ★ c) self-report d) other / no description	☐ ☐ ☐ ☐
2. Was follow up long enough for outcomes to occur a) yes, if median duration of follow-up ≥ 3 years ★ b) no, if median duration of follow-up < 3 years	☐ ☐
3. Adequacy of follow up of cohorts a) complete follow up: all subjects accounted for ★ b) subjects lost to follow up unlikely to introduce bias: number lost ≤ 20%, ★ or description of those lost suggesting no different from those followed c) follow up rate < 80% and no description of those lost d) no statement	☐ ☐ ☐ ☐

4.2.4 Outcomes of interest and definitions

The following outcomes were used to compare patients with synchronous CLM undergoing combined versus sequential hepatic resections:

1. Adverse events: perioperative mortality, overall postoperative complications, hepatectomy related complications, general complications, bile leak, bowel anastomotic leak, wound infections, cardiovascular complications, and respiratory complications
2. Perioperative outcomes: operating time in minutes (min), operative blood loss in millilitres (mL), proportion of patients needing blood transfusion, and duration of hospital stay in days
3. Overall survival and recurrence-free survival
4. Quality of life

4.2.5 Statistical analysis

For detailed explanation of the statistical analysis please refer to section 2.3.4. Analysis was conducted using Review Manager Version 5.1.[138]

Statistical analysis of binary variables was performed using the OR and was reported with 95% CI.[140] The MH method was used to combine the OR for the outcomes of interest. OR represent the odds of an adverse event occurring in the combined group compared to the sequential group, and an OR of less than one favoured the combined resection group.

Statistical analysis of continuous variables was performed using the MD and was reported with 95% CI.[140] MDs summarise the differences between the combined and sequential resection groups with respect to continuous variables, accounting for sample size, and a negative MD favoured the combined resection group.

The HR was used to compare the time-to-event outcomes ‘overall survival’ and ‘recurrence-free survival’ between the combined and sequential resection groups. The generic inverse variance method was used to combine the time-to event outcomes. An HR of less than one favoured the combined group.

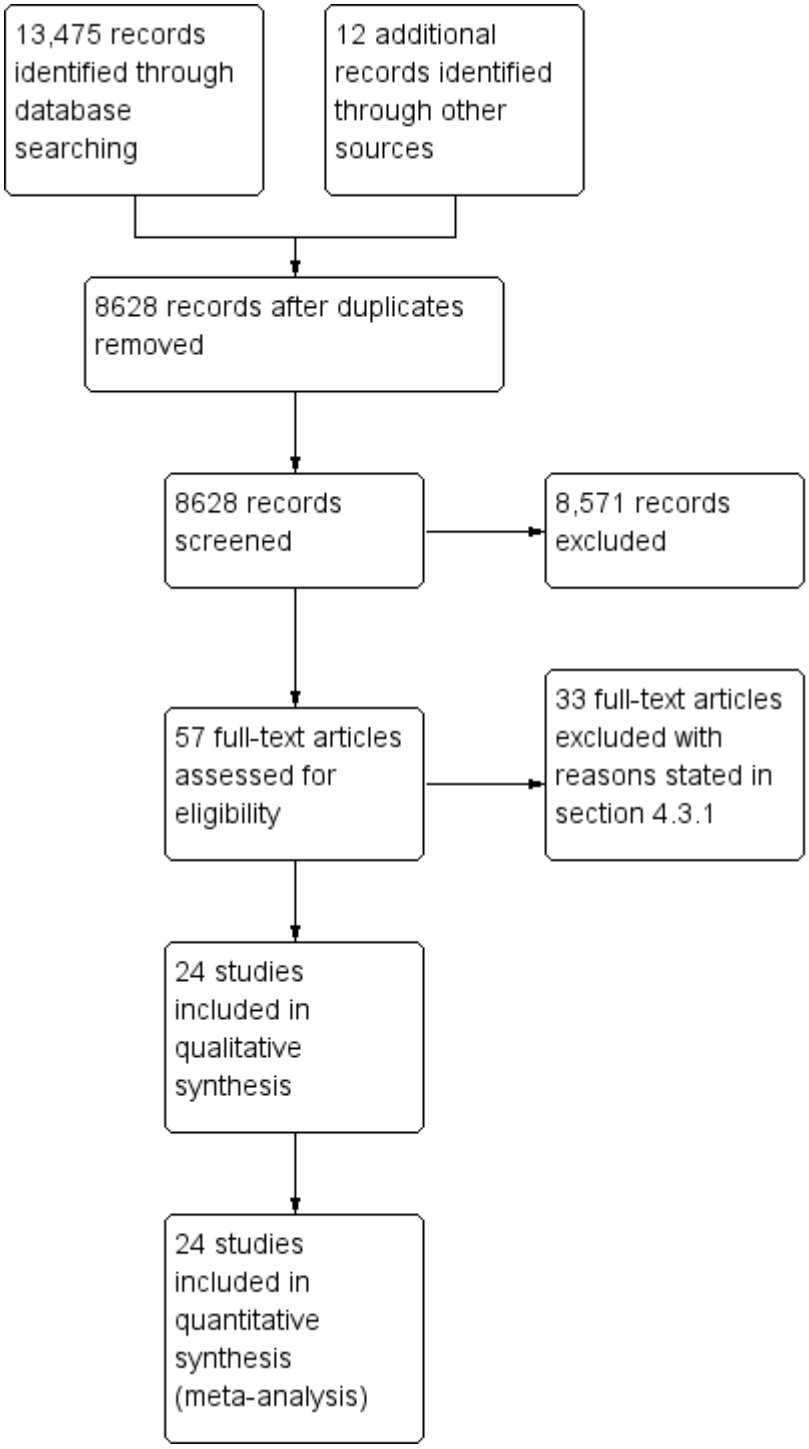
Statistical heterogeneity between studies was explored using the chi-squared test, with significance set at the $P<0.10$ level, and the amount of heterogeneity was determined by means of I-square. Three further strategies were used to quantitatively assess heterogeneity. First, graphical exploration with funnel plots was used to evaluate publication bias.[145, 147] Second, data was analysed using both random-effects and fixed-effect models. Where there was no difference between the results of random-effects and fixed-effect models that would change interpretation of the results, the results of the fixed-effect model were reported; otherwise, both the results were reported. Third, sensitivity analysis was undertaken based on the following factors: more recent studies published from 2009 onwards,[112, 162-166, 170-172] studies scoring 8 or more stars on the modified NOS,[110, 112, 162, 163, 165, 173-177] and studies including more than 60 resections in the combined resection group.[113, 164, 170, 173, 174, 177-180] The decision to perform sensitivity analysis based on the above three factors was made a priori, but the cut-off points were decided after the studies for inclusion were identified (but before any data analysis) in order to ensure adequate number of studies included in each group allowing sensitivity meta-analyses to be performed.

4.3 RESULTS

4.3.1 Eligible studies

A total of 13,475 references were identified following the search strategy described above. Twelve more references were identified for further assessment through scanning reference lists of the identified studies. The duplicates excluded between databases were 4,859. A further 8,571 clearly irrelevant references were excluded through screening titles and reading abstracts. Fifty-seven references were retrieved for further assessment. After reviewing the studies in detail, 33 were excluded for the following reasons: 7 studies were non-comparative, 11 studies included the assessment of metachronous CLM, 14 studies were either reviews, editorials, letters or abstracts, 1 study was from the same institution and authors as another included study. In total, 24 studies[110, 112, 113, 162-166, 170-185] met the inclusion criteria and were included in the meta-analysis. This is summarised in the study flow diagram in Figure 4.1.

Figure 4.1: Study flow diagram.



4.3.2 Characteristics of the included studies

All studies included in the meta-analysis were non-randomised retrospective (NRR) studies and were published between 1991 and 2010. The patients included in the combined and sequential resection groups were from a contemporary cohort of patients in 23 studies,[110, 112, 113, 162-166, 170-179, 181-185] and in one study the patients in the sequential resection group belonged to a succeeding (more recent) cohort of patients.[180] A total of 3,159 participants were included in the analysis, of which 1,381(43.7%) had combined resections and 1,778 (56.3%) had sequential resections for synchronous CLM. Only 4 studies[112, 175, 178, 180] reported the number of patients belonging in the sequential operation group who received chemotherapy between the first and second operation.

The primary tumour was in the colon for the majority of both combined and sequential resections, except for four studies: in three studies[164, 174, 178] the majority of the primary tumours of the combined resection group were rectal in origin, and in one study[166] all the primary tumours of both groups were rectal in origin. The hepatic metastatic distribution in both the combined and sequential resection groups was provided by nine studies.[112, 162, 163, 174, 175, 177, 181, 182, 185] The proportion of patients with a bilobar metastatic distribution was higher in the combined resection group only in two studies[174, 177] out of the nine, whereas, in the other seven studies[112, 162, 163, 175, 181, 182, 185] the proportion of patients with a bilobar metastatic distribution was higher in the sequential resection group.

Statistical comparison of the patient characteristics included in the combined and sequential resection groups showed no significant difference between the two groups in age (P=0.58), gender (P=0.87), number of colonic primaries (P=0.65), and number of liver metastases (P=0.3). On the other hand, compared to the combined resection group, the sequential resection group had significantly higher rate of bilobar distribution of the liver metastases (P=0.01), significantly greater proportion of major liver resections performed (P<0.001), and significantly larger size of liver metastases (P<0.001). These statistically significant differences were favouring the combined resection group, suggesting a selection bias towards a lower metastatic burden in the patients belonging in this group. The characteristics of the included studies and patient demographic data are shown in Table 4.2. The number of colon primary tumours and the burden of metastatic disease are shown in Table 4.3.

Table 4.2: Characteristics of the included studies and patient demographic data.

Author	Year	Study Design	No of patients		Age[a]		Male (n [%])		Study Quality (max: 9)
			C	S	C	S	C	S	
Brouquet, et al	2010	NRR	43	72	58(m)	56(m)	23(53)	44(61)	8
Capussotti, et al	2007	NRR	70	57	64.9	60.8	40(57)	35(61)	8
Chua, et al	2004	NRR	64	32	63	61	39(61)	18(56)	8
de Hass, et al	2010	NRR	55	173	56	58	28(51)	107(62)	8
Jaeck, et al	1999	NRR	28	31	56	60	----	----	7
Kaibori, et al	2010	NRR	32	42	65	62.3	17(53)	27(64)	9
Luo, et al	2010	NRR	129	276	58	60	76(59)	156(57)	7
Martin, et al	2009	NRR	70	160	58(m)	61(m)	38(54)	91(57)	7
Minagawa, et al	2006	NRR	142	18	----	----	----	----	5
Moug, et al	2010	NRR	32	32	69	67	18(56)	21(66)	8
Petri, et al	2010	NRR	14	29	60	64.2	8(57)	17(59)	6
Reddy, et al	2007	NRR	135	475	57	58	84(62)	277(58)	6
Scheele, et al	1991	NRR	90	42	----	----	----	----	6
Slupski, et al	2009	NRR	28	61	59.4	60.2	18(64)	34(56)	7
Tanaka, et al	2004	NRR	39	37	----	----	20(51)	25(68)	7
Taniai, et al	2006	NRR	37	8	----	----	----	----	6
Thelen, et al	2007	NRR	40	179	60.5	59.7	24(60)	96(54)	8
Turrini, et al	2007	NRR	57	62	60	59	----	----	8
Van der Pool, et	2010	NRR	8	29	----	----	----	----	6
Vassiliou, et al	2007	NRR	25	78	63	61	15(60)	47(60)	8
Vogt, et al	1991	NRR	19	17	----	----	----	----	5
Weber, et al	2003	NRR	35	62	58	60	18(51)	31(50)	7
Yan, et al	2007	NRR	73	30	60	59	33(45)	15(50)	8
Yoshidome, et	2008	NRR	116	21	----	----	83(72)	12(57)	6

Footnotes: NRR=Non-Randomised Retrospective, [a]m=median values all other values given as means, C=combined resection group, S=sequential resection group.

Table 4.3: Number of colon primary tumours and burden of metastatic disease for each included study.

Author	Colon (n [%])		Bilobar (n [%])		Pre-op metastatic size (cm)[a]		Major liver resection %	
	C	S	C	S	C	S	C	S
Brouquet, et al	25(58)	37(51)	13(30)	43(60)	2(m)	3(m)	35	67
Capussotti, et al	43(61)	37(65)	----	----	----	----	34	56
Chua, et al	27(46)	15(54)	16(25)	13(41)	3.7	3.9	16	40
de Hass, et al	43(78)	140(82)	17(31)	75(43)	3.9	3.8	----	----
Jaeck, et al	22(78)	19(61)	10(36)	18(58)	----	----	32	52
Kaibori, et al	27(84)	28(67)	7(22)	20(48)	----	----	----	----
Luo, et al	60(47)	139(50)	----	----	----	----	32	38
Martin, et al	49(70)	123(77)	----	----	3.7(m)	4(m)	47	40
Minagawa, et al	70(49)	14(78)	----	----	----	----	11	38
Moug, et al	17(53)	17(53)	----	----	----	----	22	22
Petri, et al	----	----	----	----	2.6	4.6	0	21
Reddy, et al	81(60)	367(77)	----	----	2.5	3.5	26	61
Scheele, et al	----	----	----	----	----	----	----	----
Slupski, et al	18(64)	47(77)	----	----	3.5	4.1	29	48
Tanaka, et al	24(65)	20(53)	14(36)	24(65)	2.4	5.0	13	59
Taniai, et al	----	----	----	----	----	----	----	----
Thelen, et al	34(85)	107(60)	15(38)	88(49)	----	----	38	79
Turrini, et al	33(58)	42(68)	----	----	----	----	----	----
Van der Pool, et al	0[b]	0[b]	----	----	----	----	----	----
Vassiliou, et al	22(88)	70(89)	----	----	----	----	----	----
Vogt, et al	----	----	----	----	----	----	32	53
Weber, et al	25(71)	38(61)	8(23)	42(68)	----	----	31	52
Yan, et al	58(79)	18(60)	50(68)	10(33)	3.8	5.9	74	73
Yoshidome, et al	67(58)	11(52)	----	15(71)	----	----	----	----

Footnotes: C=combined resection group, S=sequential resection group, [a]m=median values all other values given as means, [b]all cases were rectal primaries.

4.3.3 Overall results of meta-analysis

4.3.3.1. Adverse events

The overall meta-analysis comparing combined versus sequential resections for synchronous CLM showed no significant difference for any of the postoperative adverse events. Also, analysis with funnel plots showed no evidence of significant publication bias for these outcomes. The adverse events reported were:

- Perioperative mortality: no significant difference (Figure 4.2; combined 1.5%, sequential 1.2%; OR=1.67, 95% CI 0.86, 3.24; P=0.13), with no evidence of heterogeneity (P=0.31; I-square 15%) and no evidence of publication bias (Figure 4.3).

Figure 4.2: Overall meta-analysis - forest plot for the outcome perioperative mortality. There was no statistically significant difference in the proportion of people with perioperative mortality between the combined versus sequential operations.

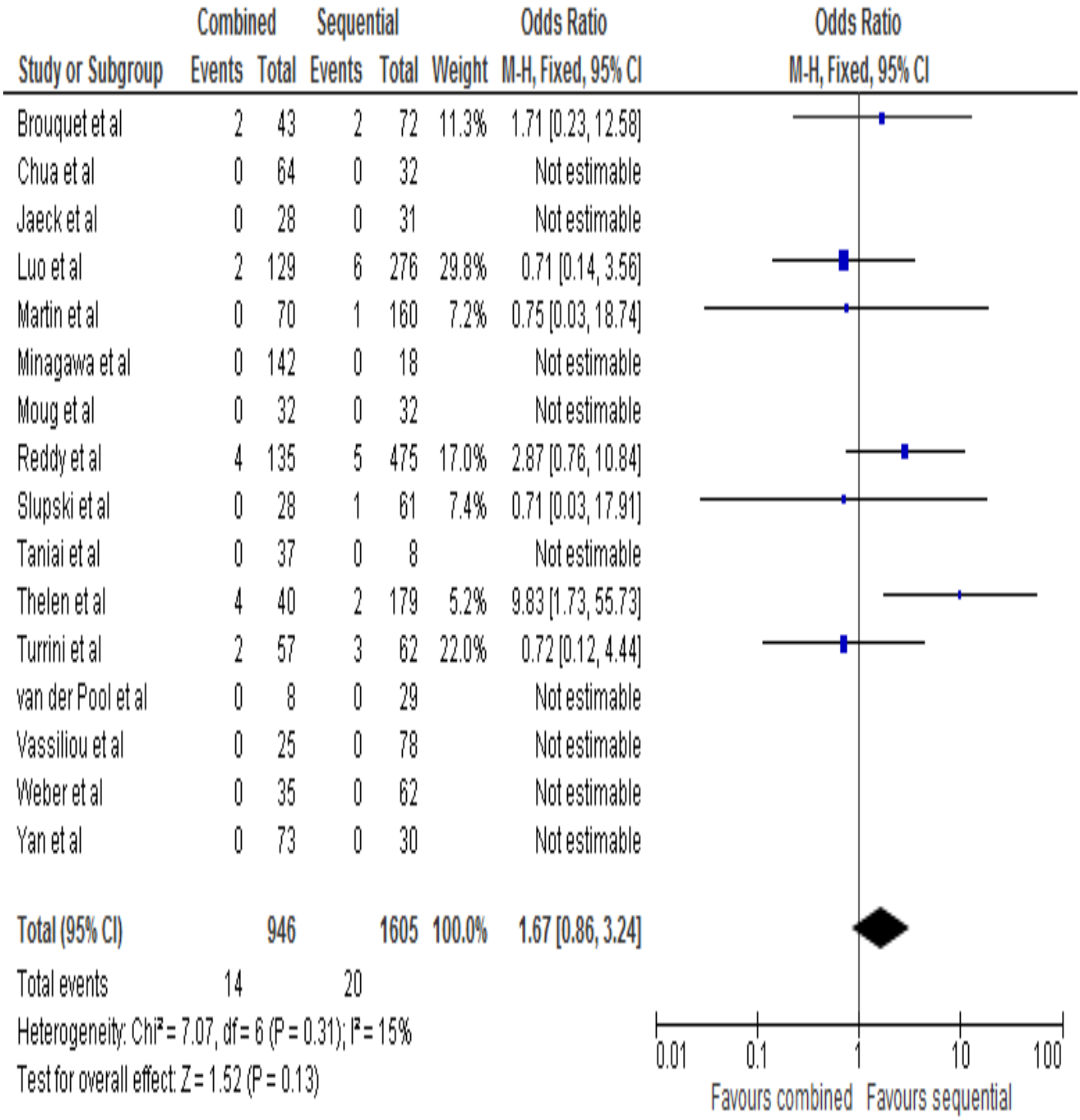
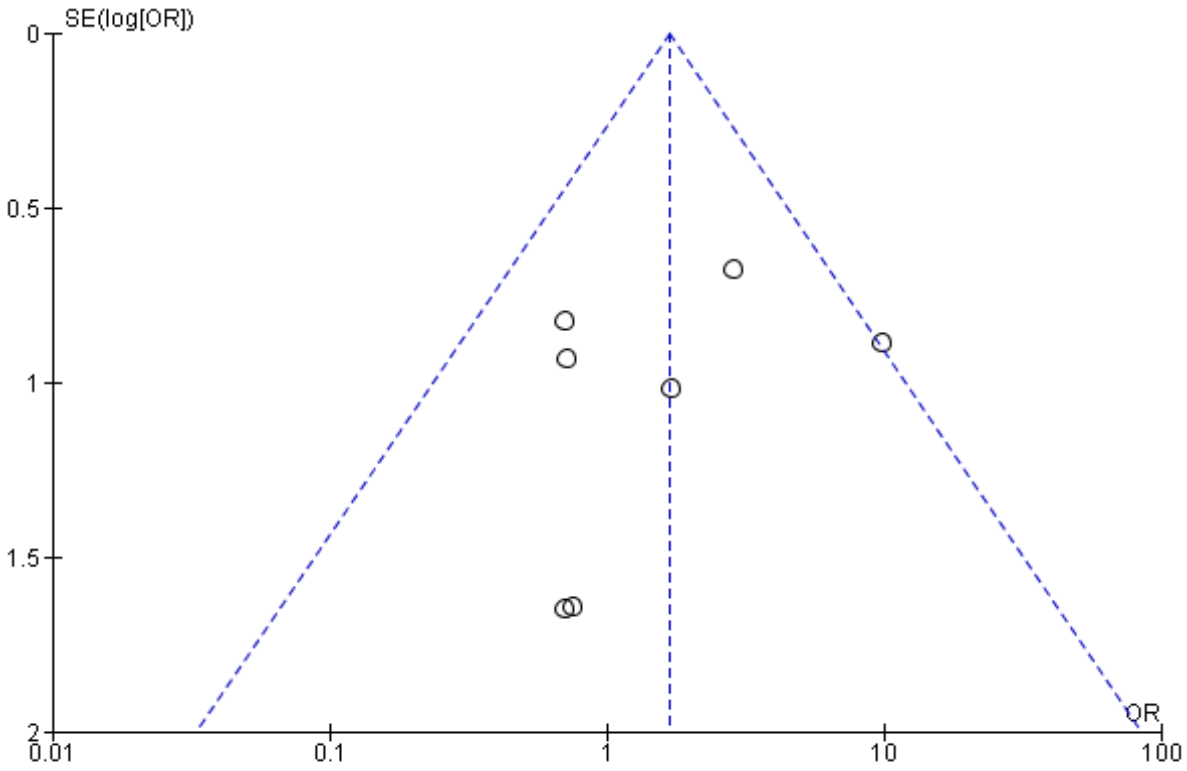


Figure 4.3: Overall meta-analysis - funnel plot for the outcome perioperative mortality. There was no evidence of publication bias.



- Overall postoperative complications: no significant difference (Figure 4.4; combined 36%, sequential 37%; OR=0.94, 95% CI 0.78, 1.12; P=0.47), with evidence of heterogeneity (P=0.02; I-square 47%) and no evidence of publication bias (Figure 4.5).

Figure 4.4: Overall meta-analysis - forest plot for the outcome overall postoperative complications. There was no statistically significant difference in the number of overall postoperative complications between the combined and sequential procedure.

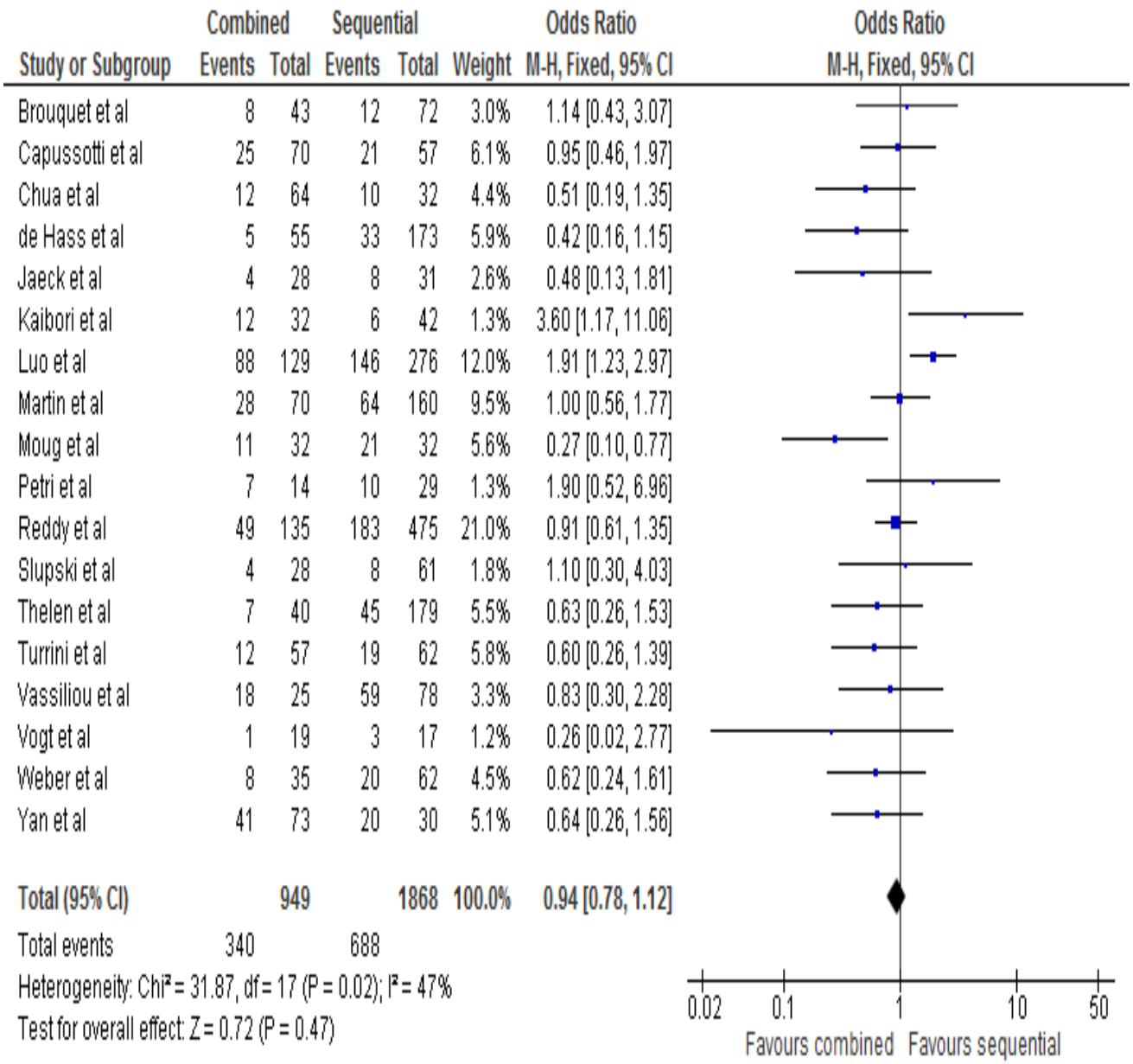
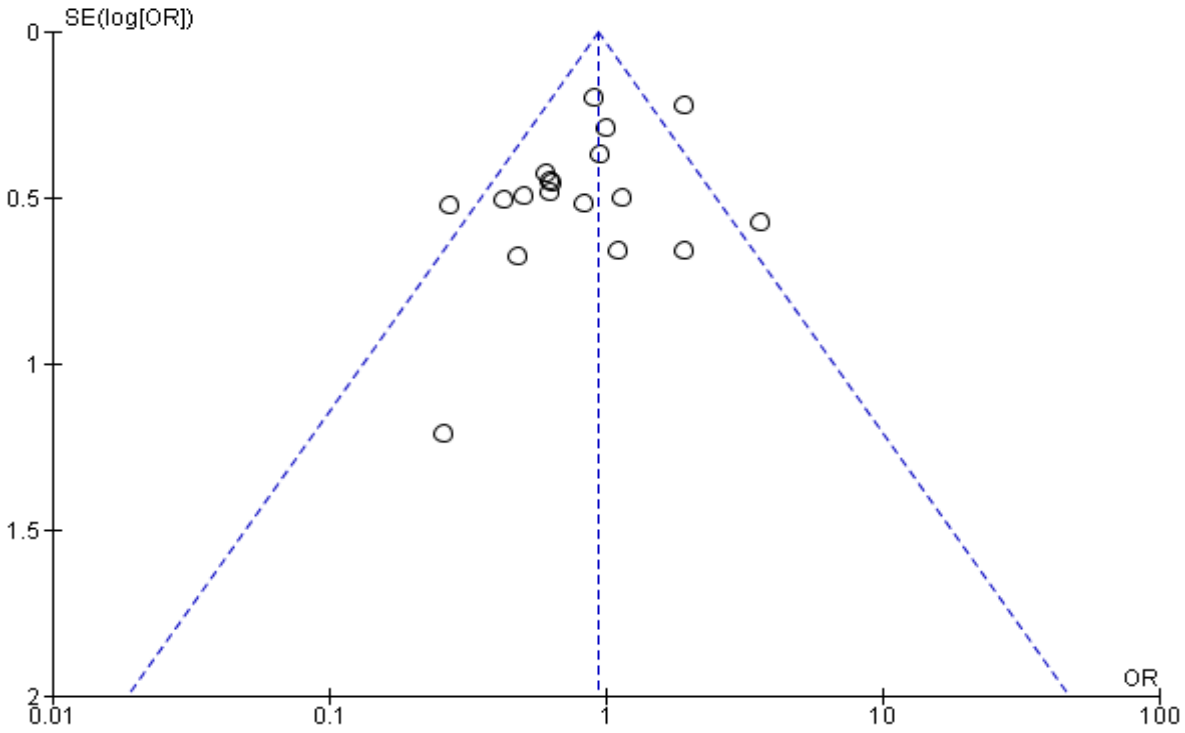


Figure 4.5: Overall meta-analysis - funnel plot for the outcome overall postoperative complications. There was no evidence of publication bias.



- Hepatectomy related complications: no significant difference (Figure 4.6; combined 11%, sequential 11%; OR=0.99, 95% CI 0.69, 1.43; P=0.97), with no evidence of heterogeneity (P=0.36; I-square 9%) and no evidence of publication bias (Figure 4.7).

Figure 4.6: Overall meta-analysis - forest plot for the outcome hepatectomy related complications. There was no statistically significant difference in the number of hepatectomy related complications between the combined and sequential procedure.

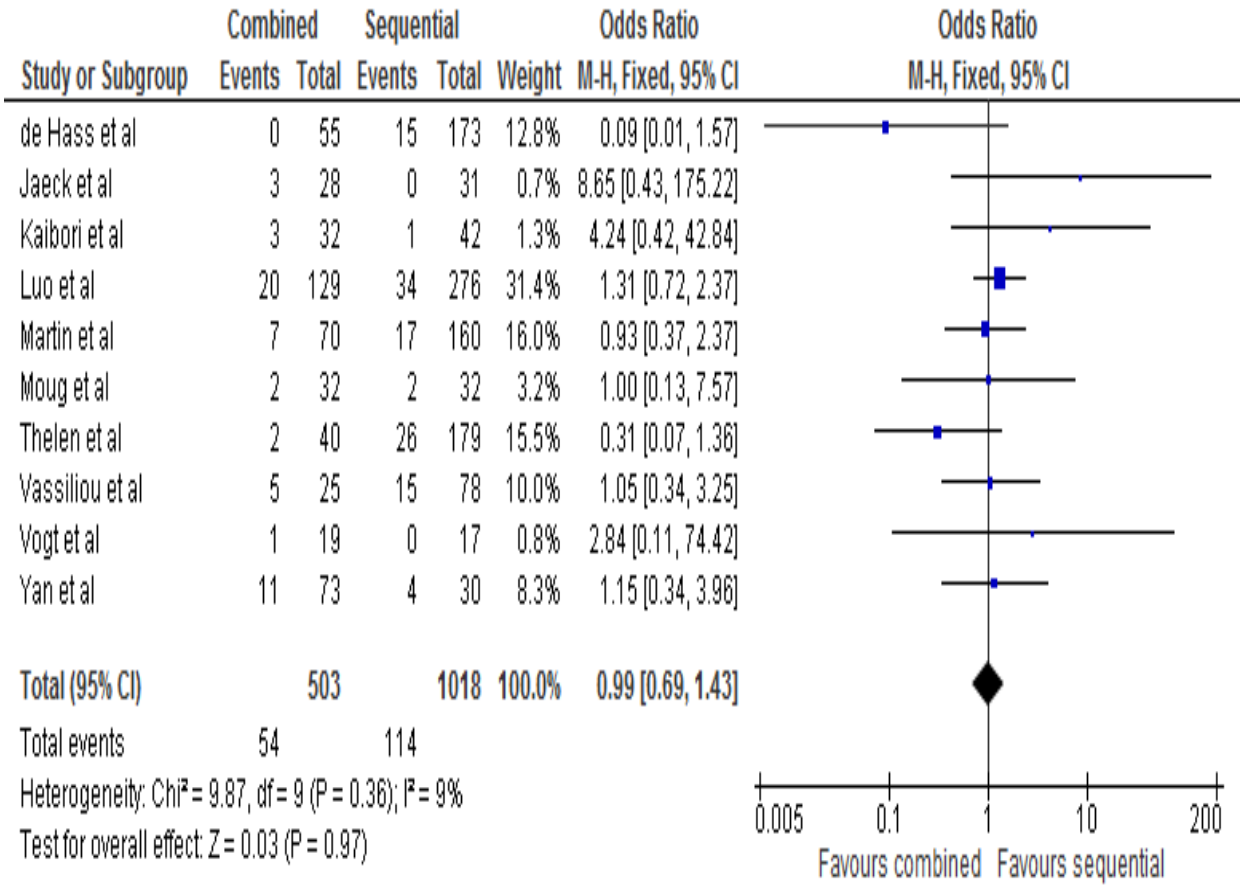
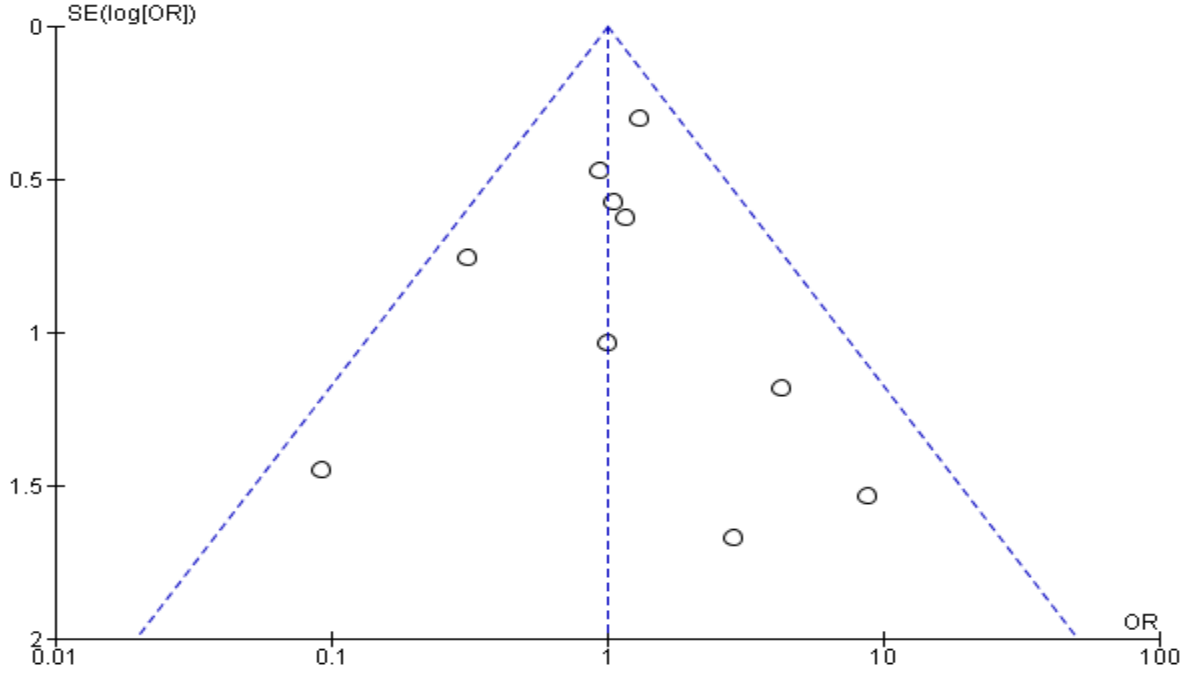


Figure 4.7: Overall meta-analysis - funnel plot for the outcome hepatectomy related complications. There was no evidence of publication bias.



- General complications: no significant difference (Figure 4.8; combined 17%, sequential 13%; OR=1.10, 95% CI 0.81, 1.50; P=0.54), with evidence of heterogeneity (P=0.02; I-square 56%) and no evidence of publication bias (Figure 4.9).

Figure 4.8: Overall meta-analysis - forest plot for the outcome general complications. There was no statistically significant difference in the number of general complications between the combined and sequential group, with evidence of heterogeneity.

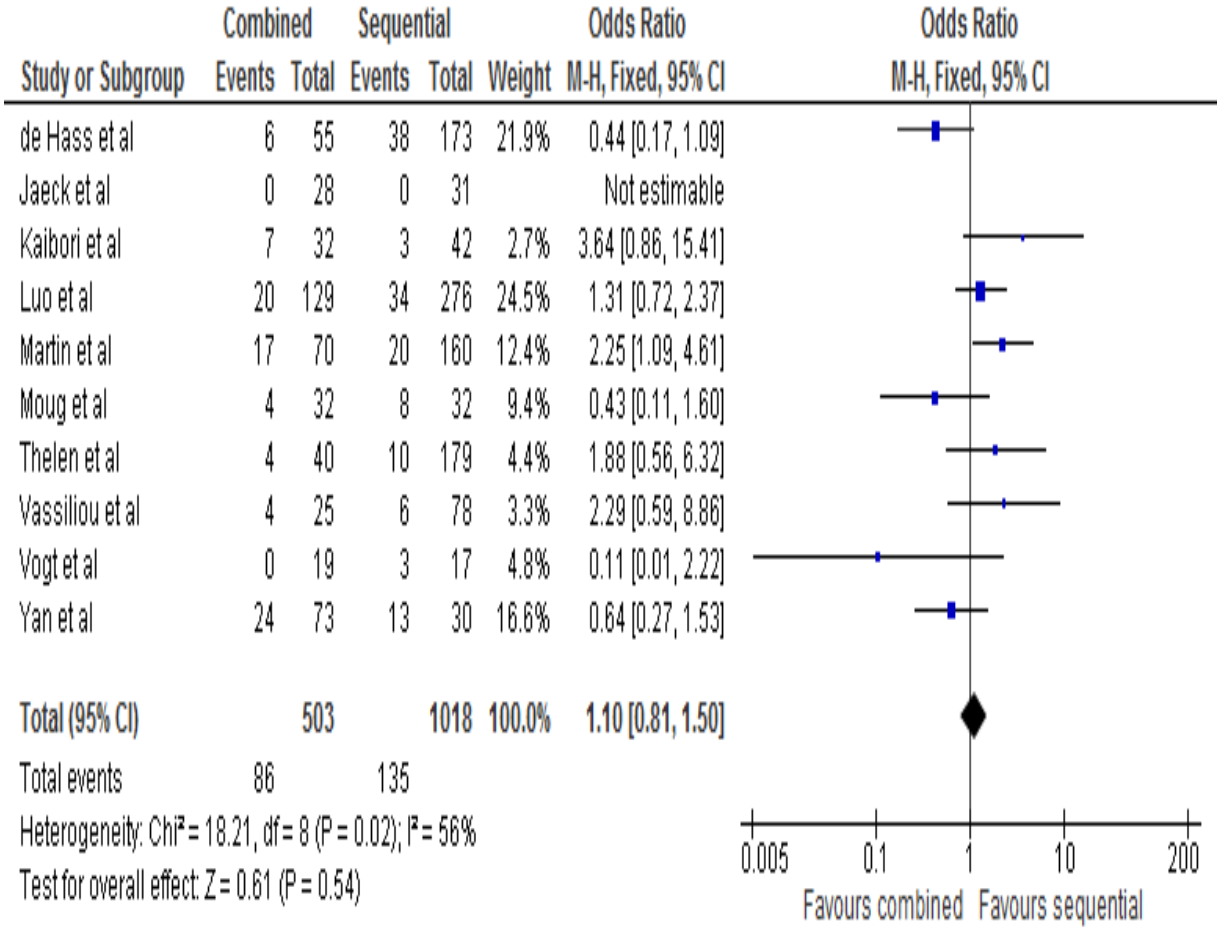
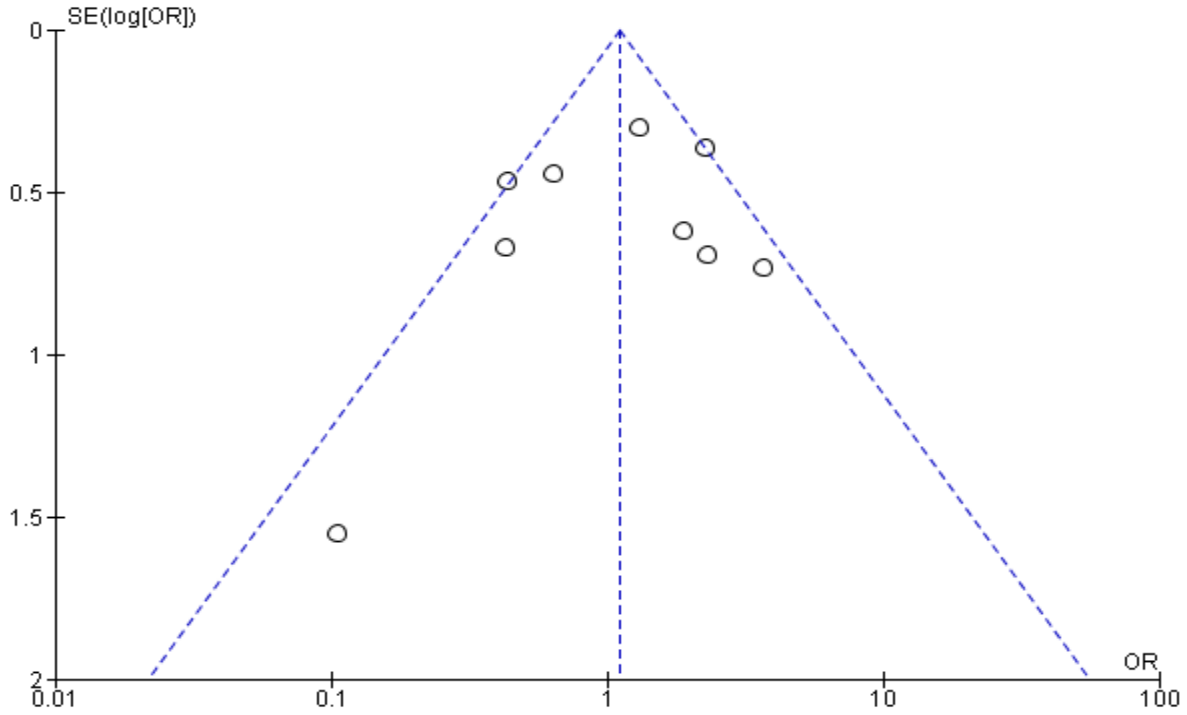


Figure 4.9: Overall meta-analysis - funnel plot for the outcome general complications. There was no evidence of publication bias.



- Bile leak: no significant difference (Figure 4.10; combined 4.1%, sequential 6.3%; OR=0.76, 95% CI 0.42, 1.39; P=0.37), with no evidence of heterogeneity (P=0.55; I-square 0%) and no evidence of publication bias (Figure 4.11).

Figure 4.10: Overall meta-analysis - forest plot for the outcome bile leak. There was no statistically significant difference in the number of patients having a bile leak between the combined and sequential resection group.

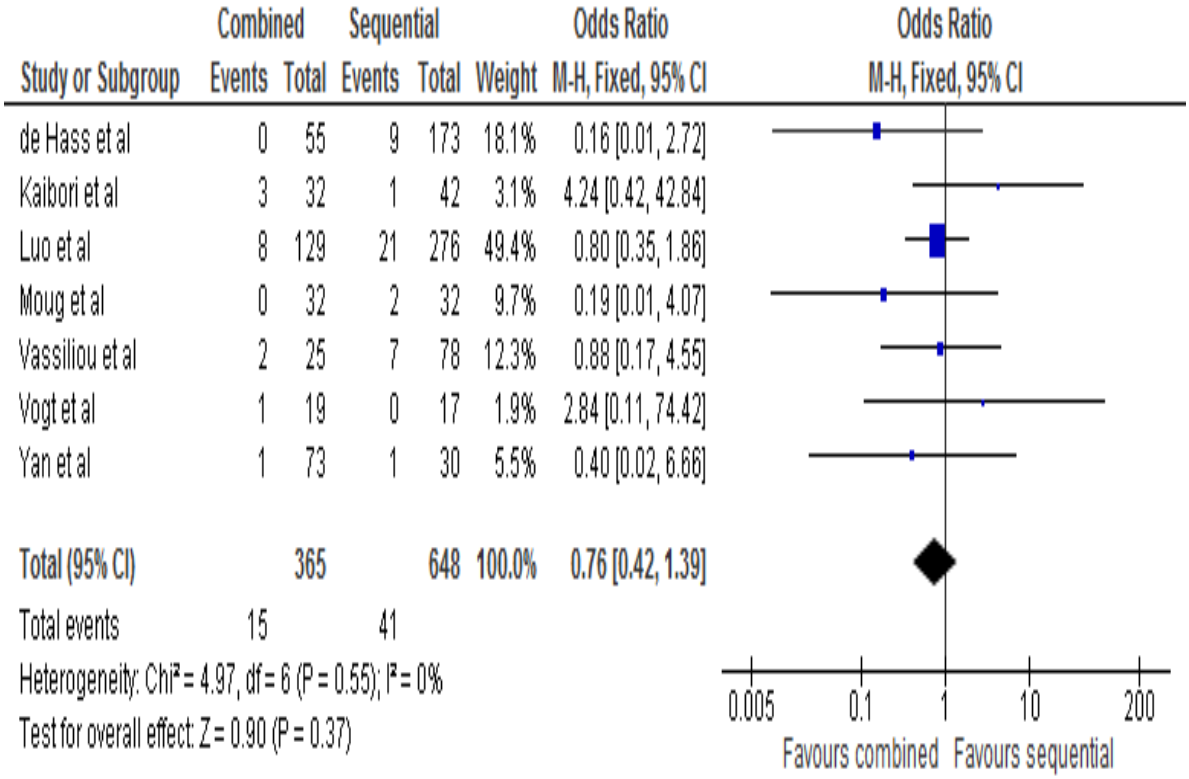
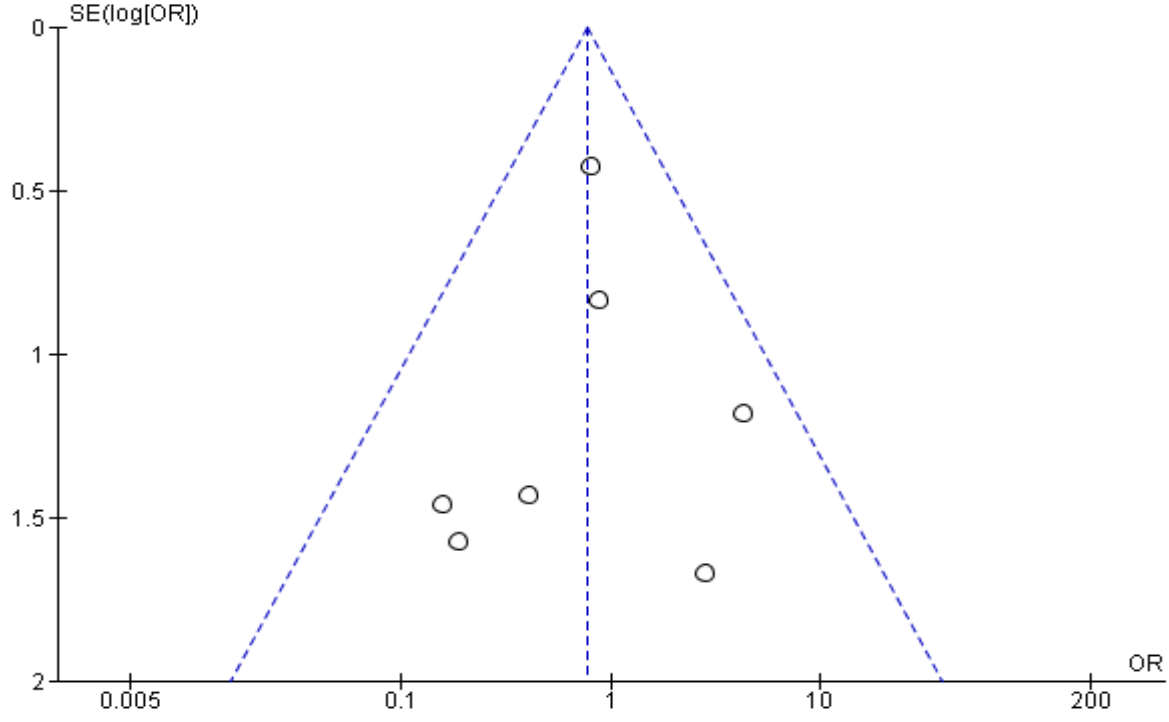


Figure 4.11: Overall meta-analysis - funnel plot for the outcome bile leak. There was no evidence of publication bias.



- Bowel anastomotic leak: no significant difference (Figure 4.12; combined 2.4%, sequential 2.1%; OR=1.15, 95% CI 0.47, 2.82; P=0.77), with no evidence of heterogeneity (P=0.42; I-square 0%) and no evidence of publication bias (Figure 4.13).

Figure 4.12: Overall meta-analysis - forest plot for the outcome bowel anastomotic leak. There was no statistically significant difference in the number of patients having a bowel anastomotic leak between the combined and sequential resection group.

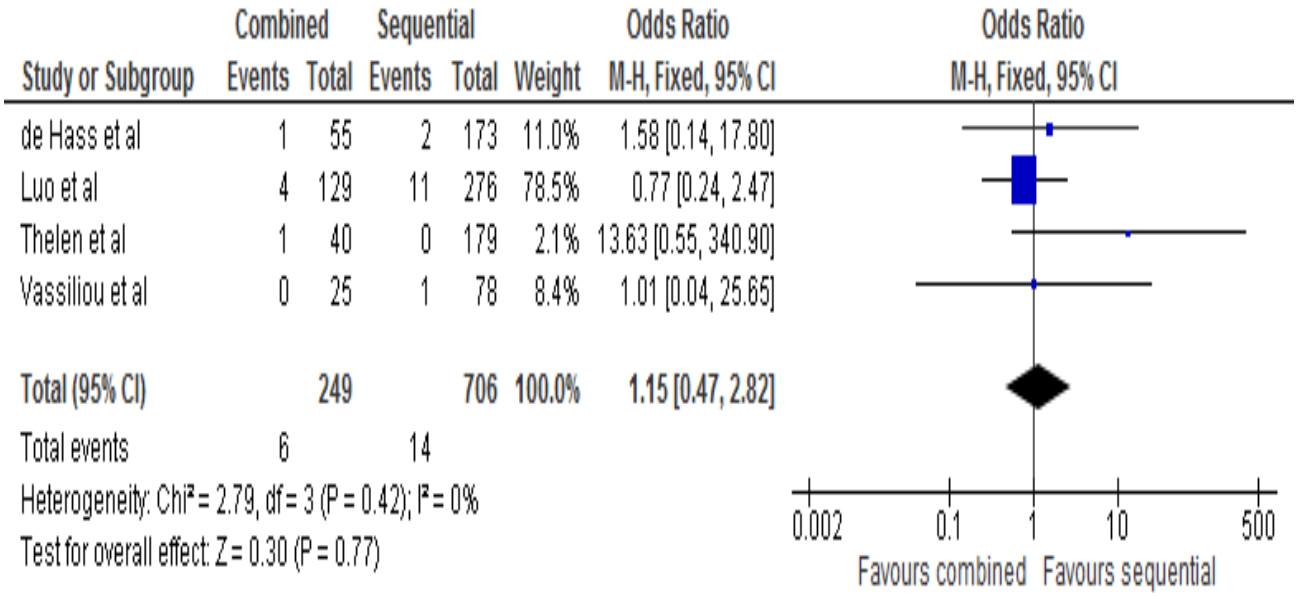
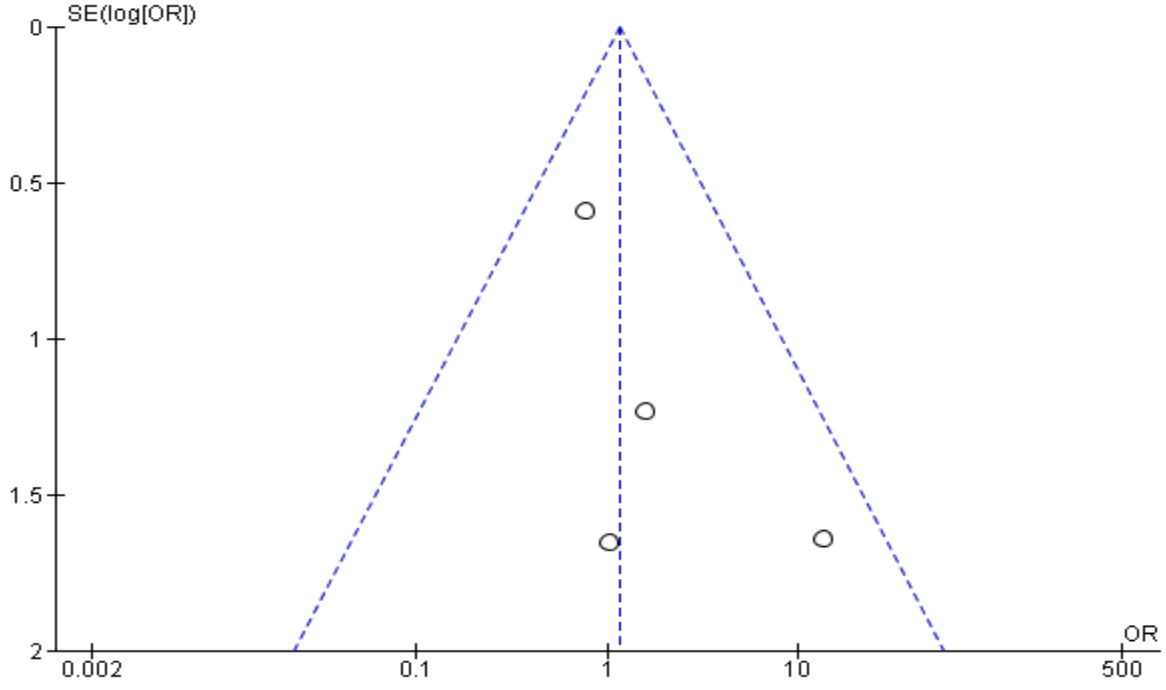


Figure 4.13: Overall meta-analysis - funnel plot for the outcome bowel anastomotic leak. There was no evidence of publication bias.



- Wound infections: no significant difference (Figure 4.14; combined 8.7%, sequential 4.6%; OR 1.41, 95% CI 0.82, 2.41; P=0.22), with no evidence of heterogeneity (P=0.79; I-square 0%) and no evidence of publication bias (Figure 4.15).

Figure 4.14: Overall meta-analysis - forest plot for the outcome wound infections. There was no statistically significant difference in the number of patients having a wound infection between the combined and sequential resection group.

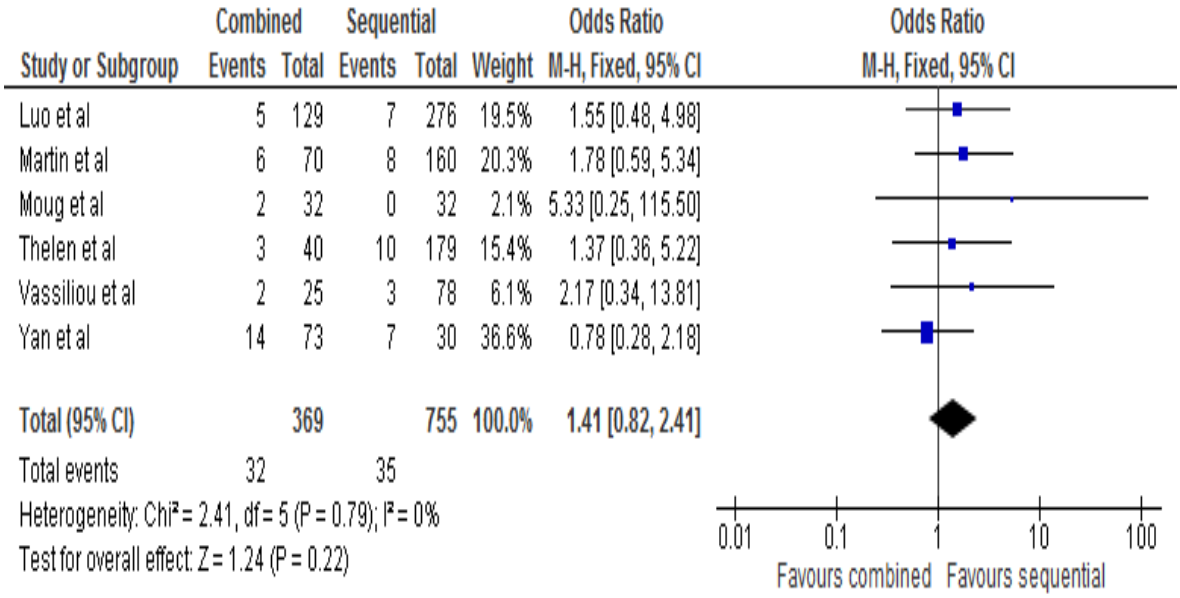
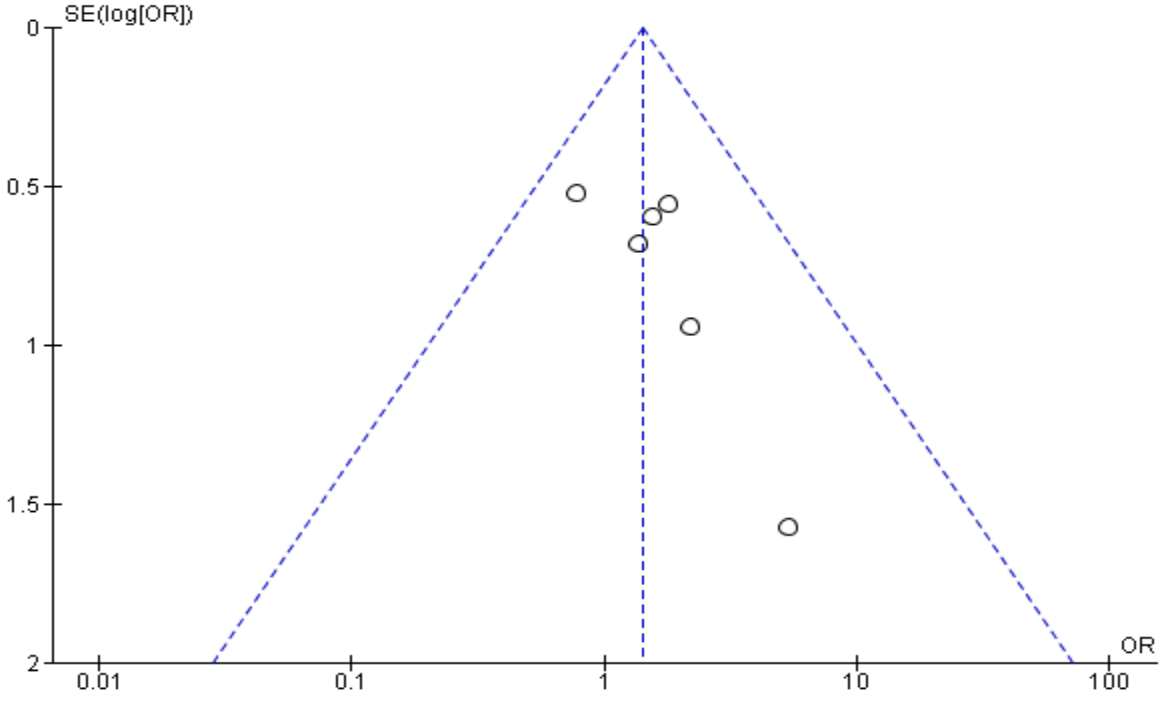


Figure 4.15: Overall meta-analysis - funnel plot for the outcome wound infections. There was no evidence of publication bias.



- Cardiovascular complications: no significant difference (Figure 4.16; combined 6.6%, sequential 6.6%; OR 1.16, 95% CI 0.65, 2.07; P=0.62), with no evidence of heterogeneity (P=0.42; I-square 0%) and no evidence of publication bias (Figure 4.17).

Figure 4.16: Overall meta-analysis - forest plot for the outcome cardiovascular complications. There was no statistically significant difference in the number of cardiovascular complications between the combined and sequential group.

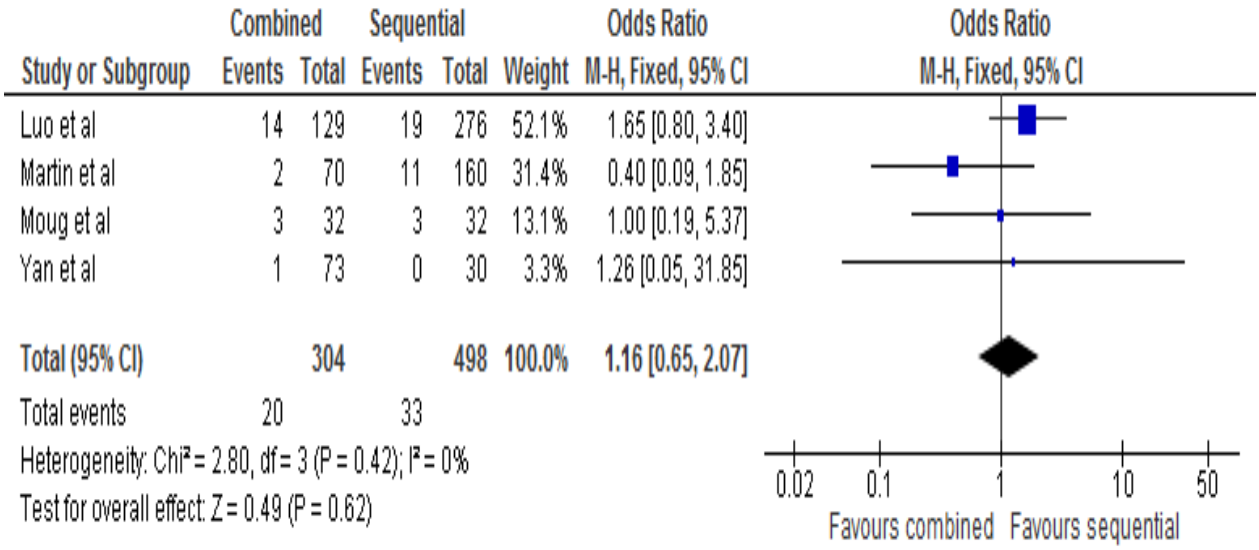
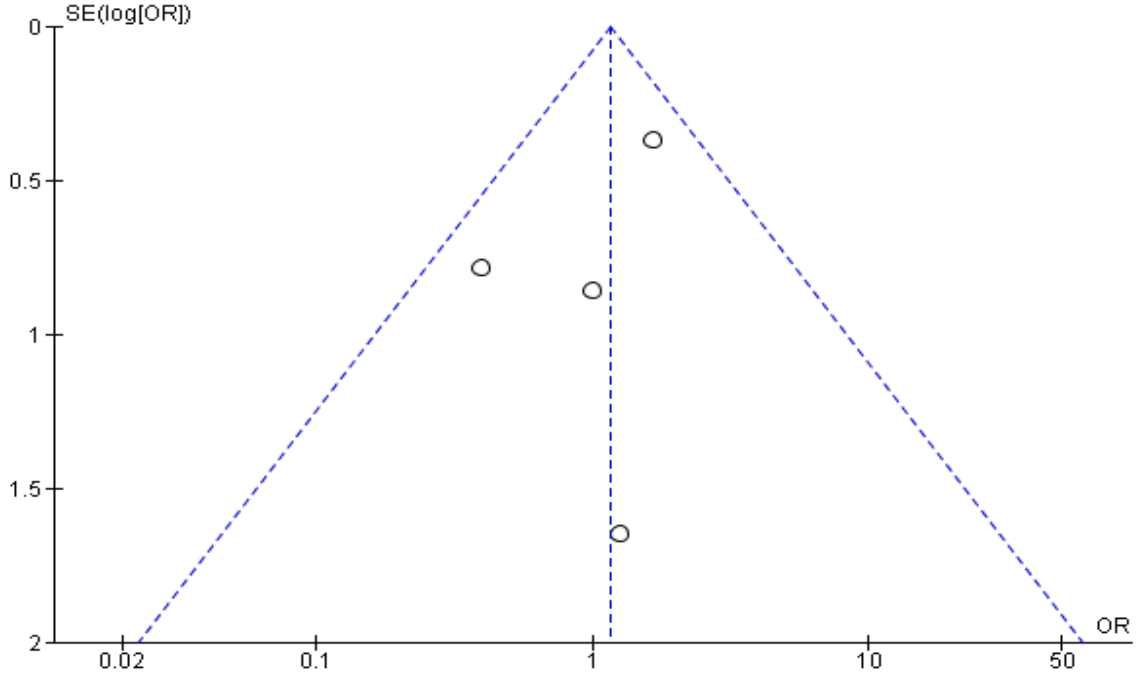


Figure 4.17: Overall meta-analysis - funnel plot for the outcome cardiovascular complications. There was no evidence of publication bias.



- Respiratory complications: no significant difference (Figure 4.18; combined 9.3%, sequential 10.7%; OR 0.85, 95% CI 0.58, 1.27; P=0.43), with no evidence of heterogeneity (P=0.23; I-square 25%) and no evidence of publication bias (Figure 4.19).

Figure 4.18: Overall meta-analysis - forest plot for the outcome respiratory complications. There was no statistically significant difference in the number of respiratory complications between the combined and sequential resection group.

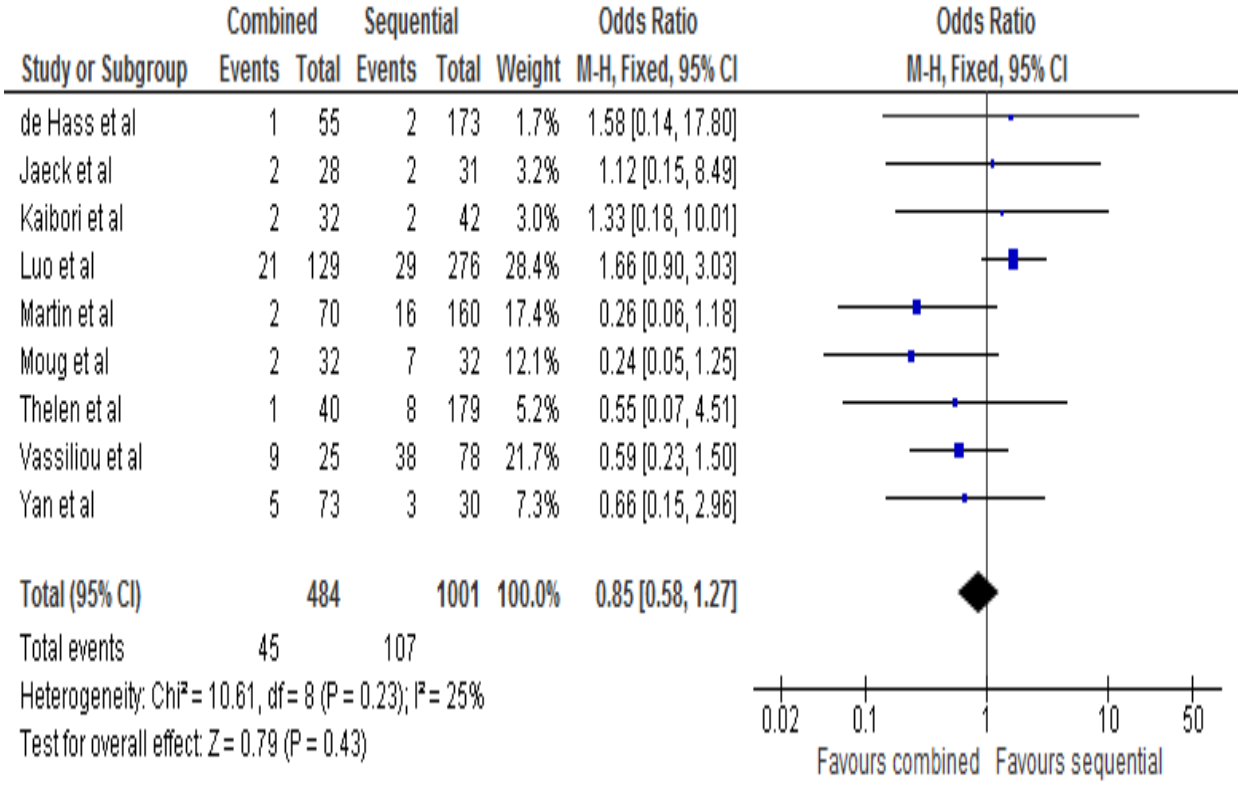
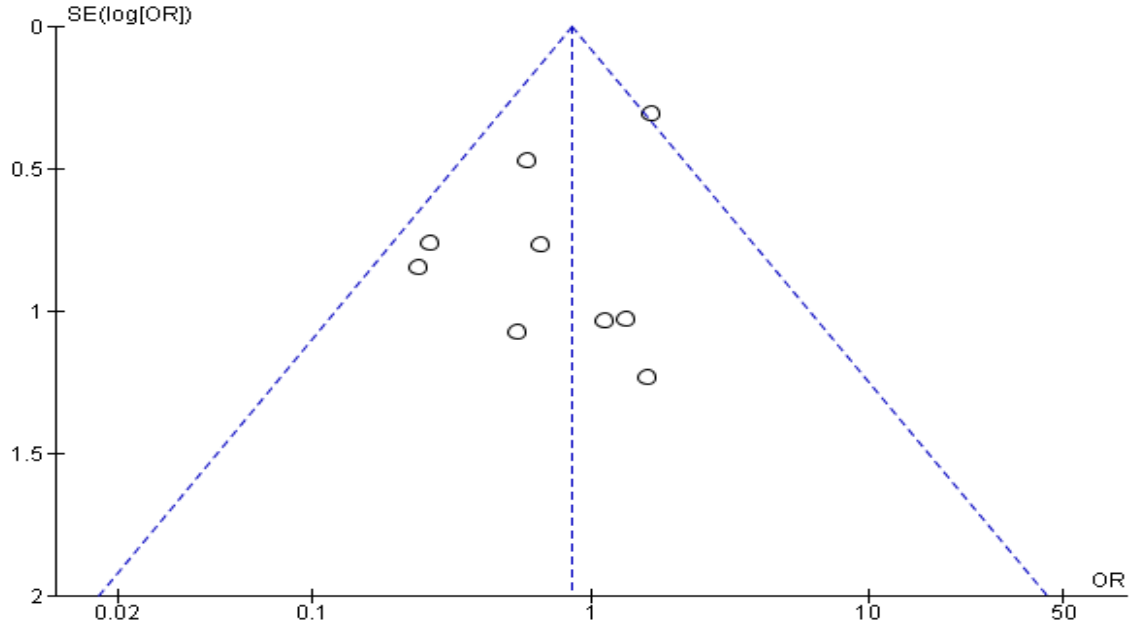


Figure 4.19: Overall meta-analysis - funnel plot for the outcome respiratory complications. There was no evidence of publication bias.



4.3.3.2. Perioperative outcomes

Operating time was reported by eight studies.[110, 164, 170, 172, 175, 181, 182, 185] The operating time was the total operating time for both procedures of the sequential resection group. Meta-analysis of this outcome using a random-effects model showed no significant difference between the combined and sequential resection groups (Figure 4.20; MD -23.83 min, 95% CI -85.04, 37.38; P=0.45); whereas meta-analysis using the fixed-effect model showed the combined resection group to have significantly shorter operating time compared to the sequential resection group (Figure 4.21; MD -37.94 min, 95% CI -47.08, -28.80, P<0.001). The reason for the difference between the two models was the significant heterogeneity between studies for this outcome (P<0.001, I-square 98%). Although, the studies are symmetrical around the vertical axis on the funnel plot for operating time (Figure 4.22), they are much spread and all of them fall out of the 95% CI lines. The random-effects model was used for the interpretation of this outcome because it takes into consideration the heterogeneity between studies and gives a more conservative effect estimate.

Figure 4.20: Overall meta-analysis - forest plot for the outcome operating time using the random-effects model. There was no statistically significant difference in operating time between the combined and sequential resection groups using the random-effects model, with significant heterogeneity between studies.

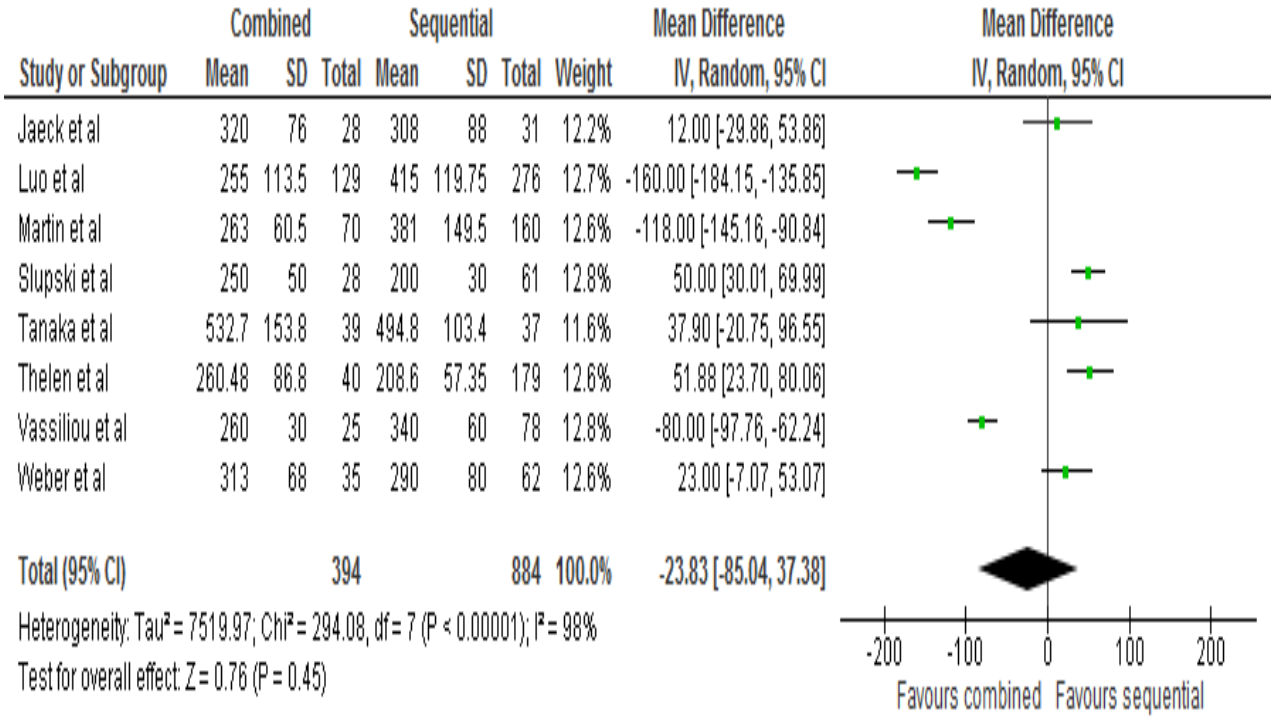


Figure 4.21: Overall meta-analysis - forest plot for the outcome operating time using the fixed-effect model. The combined resection group had significantly shorter operating time compared to the sequential resection group using the fixed-effect model, with significant heterogeneity between studies.

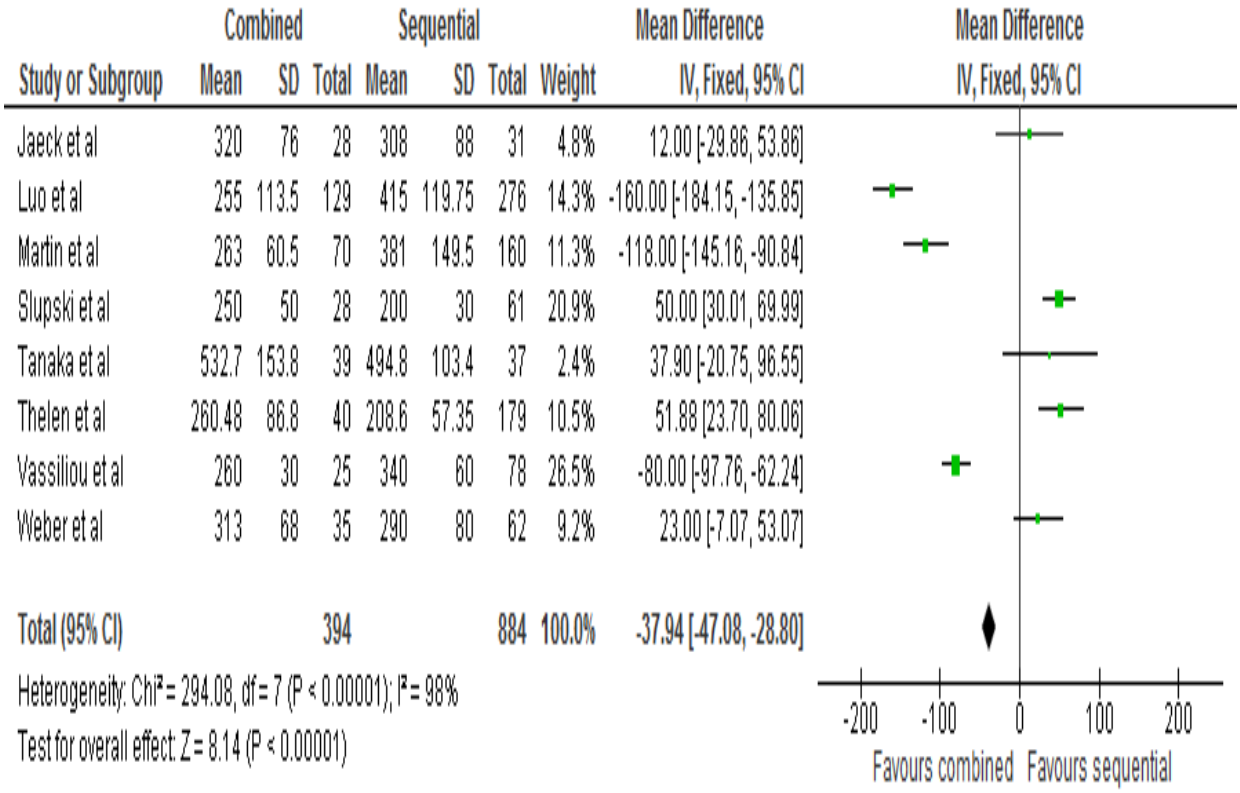
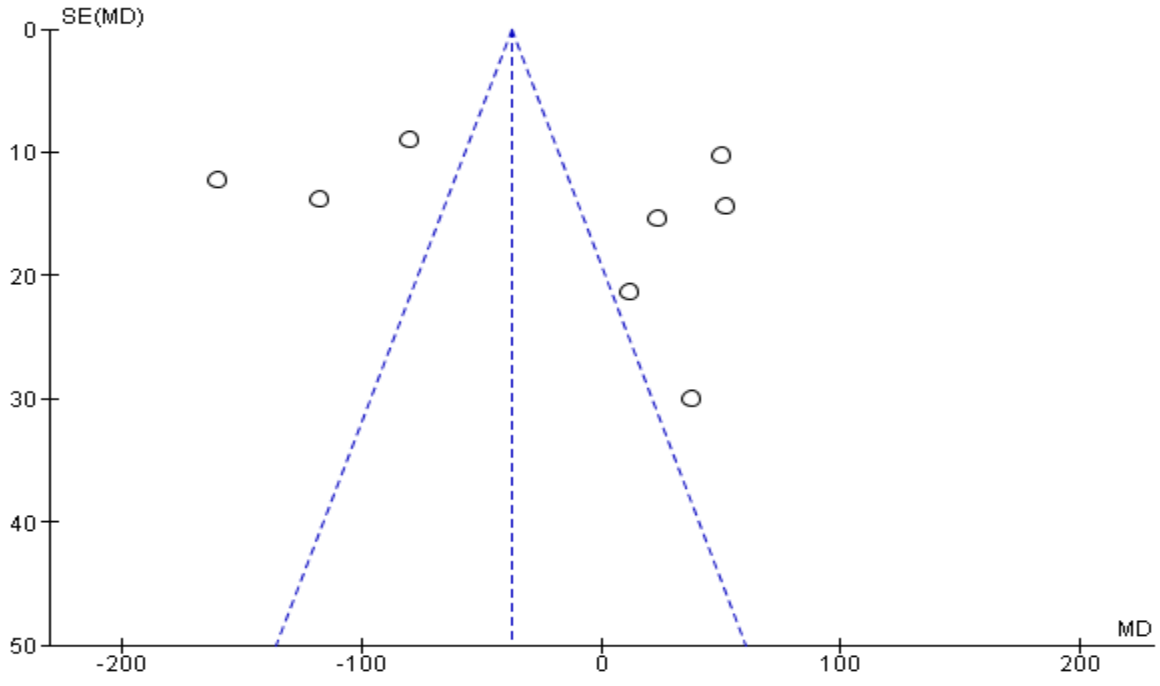


Figure 4.22: Overall meta-analysis - funnel plot for the outcome operating time. Although the studies are much spread and all of them fall out of the 95% CI lines, there is no evidence of publication bias.



Hepatic vascular occlusion time was reported by four studies.[172, 175, 181, 185] The hepatic vascular occlusion time was the total hepatic vascular occlusion time for both procedures of the sequential resection group. Meta-analysis of this outcome using a random-effects model showed no significant difference between the combined and sequential resection groups (Figure 4.23; MD -2.56 min, 95% CI -11.15, 6.03; P=0.56); whereas meta-analysis using the fixed-effect model showed the combined resection group to have significantly shorter hepatic vascular occlusion time compared to the sequential resection group (Figure 4.24; MD -5.90 min, 95% CI -7.85, -3.96, P<0.001). The reason for the difference between the two models was the significant heterogeneity between studies for this outcome (P<0.001, I-square 93%). Three studies are symmetrical around the vertical axis on the funnel plot for hepatic vascular occlusion time (Figure 4.25) but one study is an outlier and falls out of the 95% CI lines. The random-effects model was used for the interpretation of this outcome because it takes into consideration the heterogeneity between studies and gives a more conservative effect estimate.

Figure 4.23: Overall meta-analysis - forest plot for the outcome hepatic vascular occlusion time using the random-effects model. There was no statistically significant difference in hepatic vascular occlusion time between the combined and sequential resection groups using the random-effects model, with significant heterogeneity between studies.

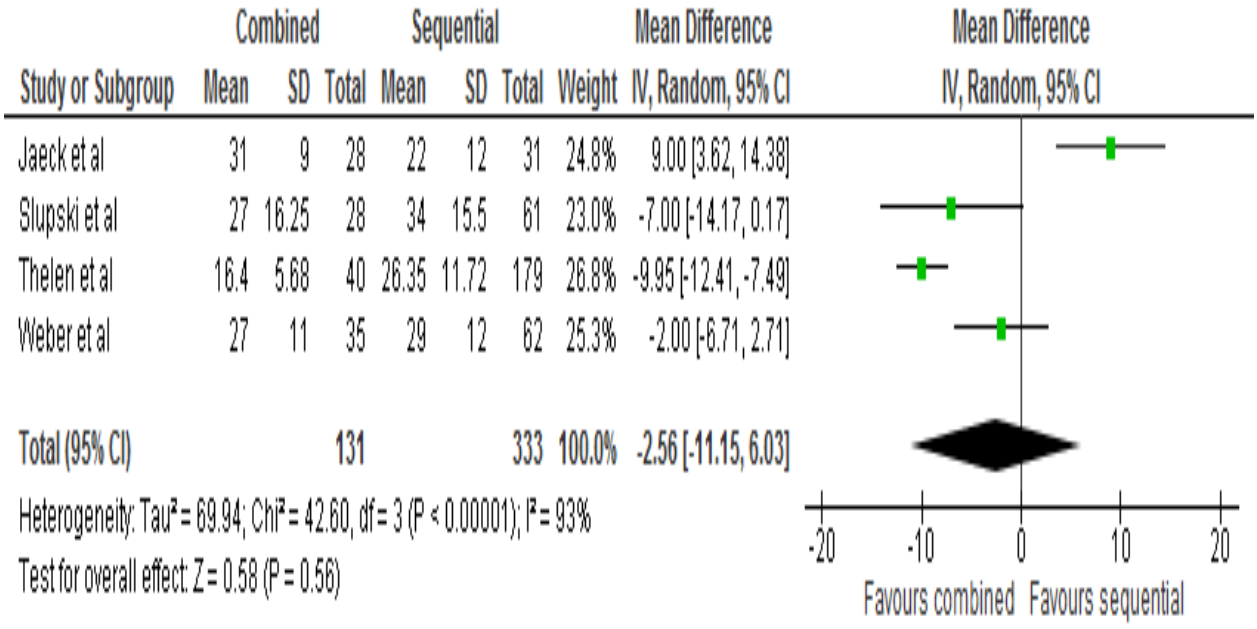


Figure 4.24: Overall meta-analysis - forest plot for the outcome hepatic vascular occlusion time using the fixed-effect model. The combined resection group had significantly shorter hepatic vascular occlusion time compared to the sequential resection group using the fixed-effect model, with significant heterogeneity between studies.

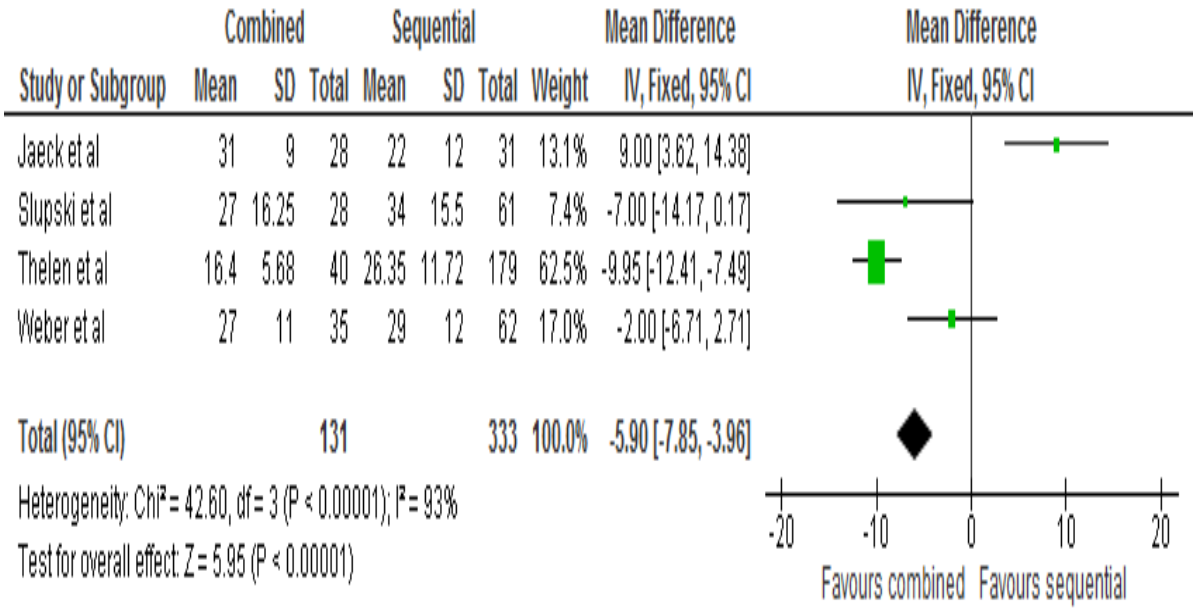
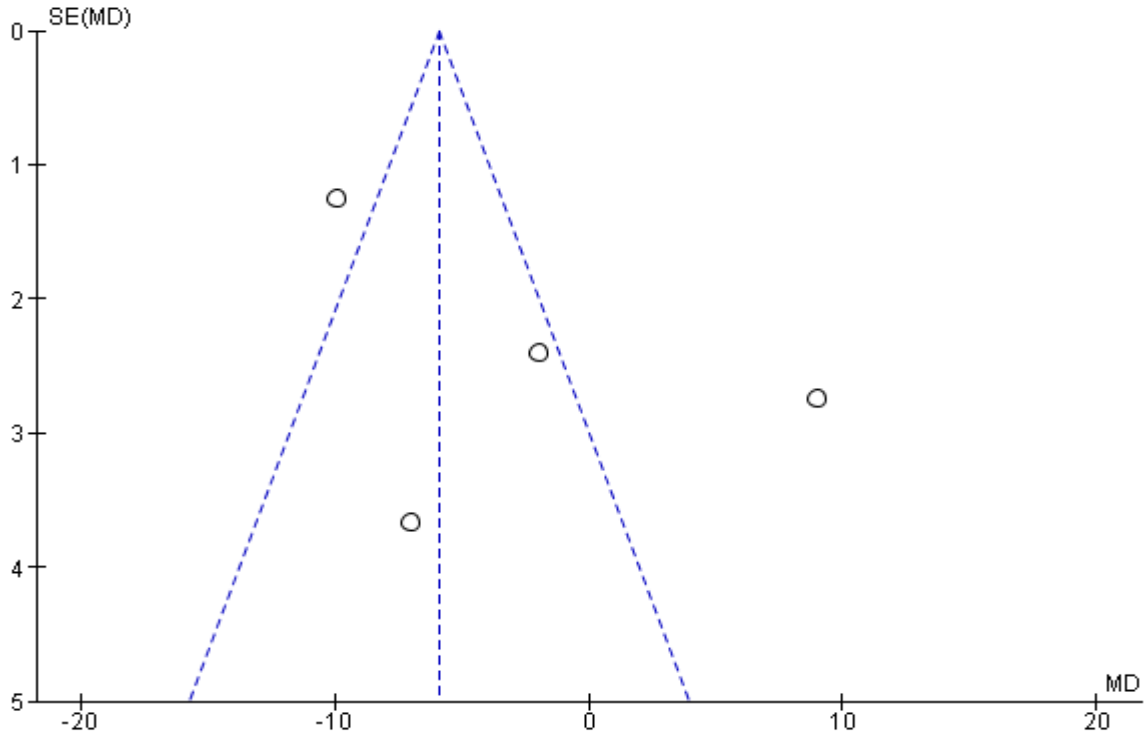


Figure 4.25: Overall meta-analysis - funnel plot for the outcome hepatic vascular occlusion time. Three studies are symmetrical around the vertical axis on the funnel plot for hepatic vascular occlusion time, but one study is an outlier and falls out of the 95% CI lines.



Operative blood loss was reported by seven studies[112, 163-165, 170, 172, 182]. The operative blood loss was the total operative blood loss for both surgeries of the sequential resection group. Meta-analysis using the random-effects model showed no significant difference between the two groups for this outcome (Figure 4.26; MD -128.37 mL, 95% CI -279.28, 22.53, P=0.10); using the fixed-effect model showed the combined resection group to have significantly lower operative blood loss compared to the sequential resection group (Figure 4.27; MD -221.46 mL, 95% CI -257.59, -185.32; P<0.001). The reason for the difference between the two models was the significant heterogeneity between studies for this outcome (P<0.001, I-square 85%). The funnel plot showed one study,[172] which favoured the sequential resection group for this outcome, to be well out of the 95% CI lines (Figure 4.28). The random-effects model was preferred for the interpretation of this outcome because it gives a more conservative effect estimate.

Figure 4.26: Overall meta-analysis - forest plot for the outcome operative blood loss using the random-effects model. There was no statistically significant difference in operative blood loss between the combined and sequential resection groups when using the random-effects model, with significant heterogeneity between studies.

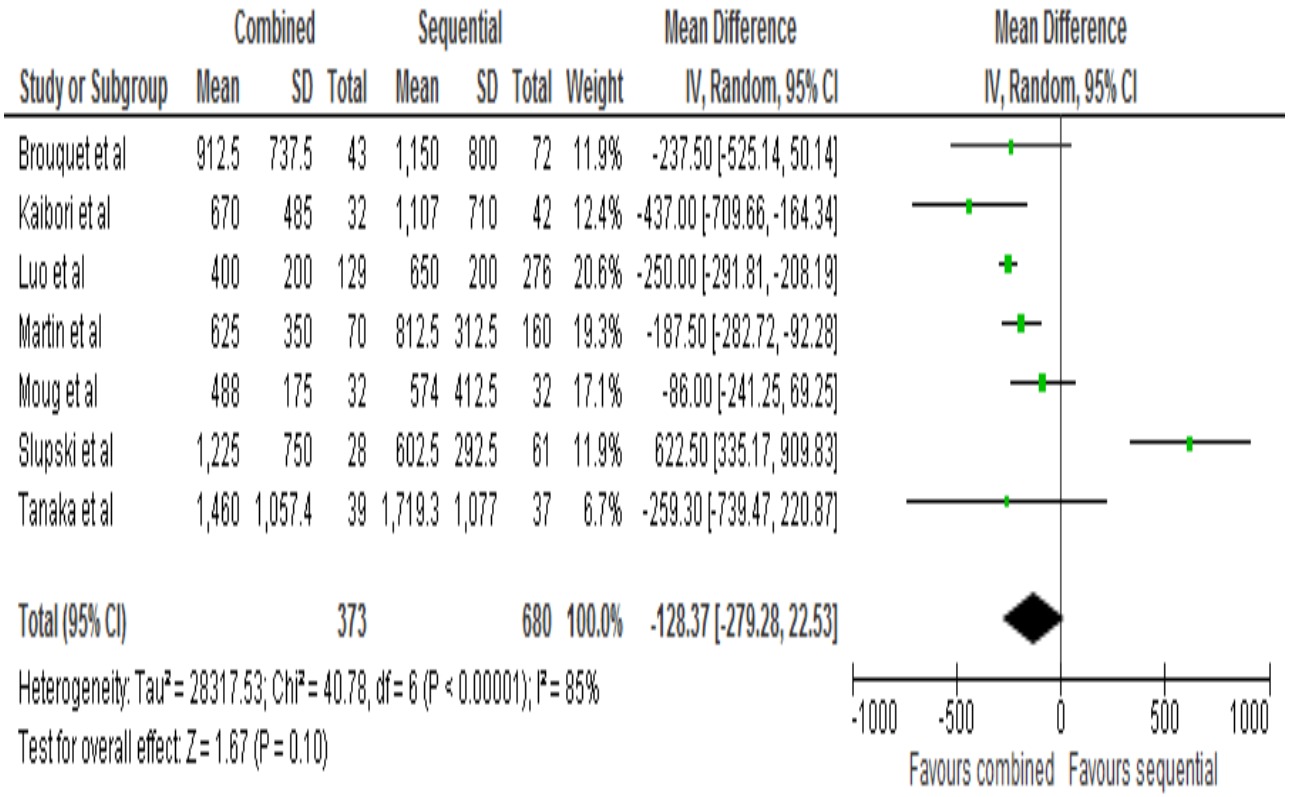


Figure 4.27: Overall meta-analysis - forest plot for the outcome operative blood loss using the fixed-effect model. The combined resection group had significantly lower operative blood loss compared to the sequential resection group when using the fixed-effect model, with significant heterogeneity between studies.

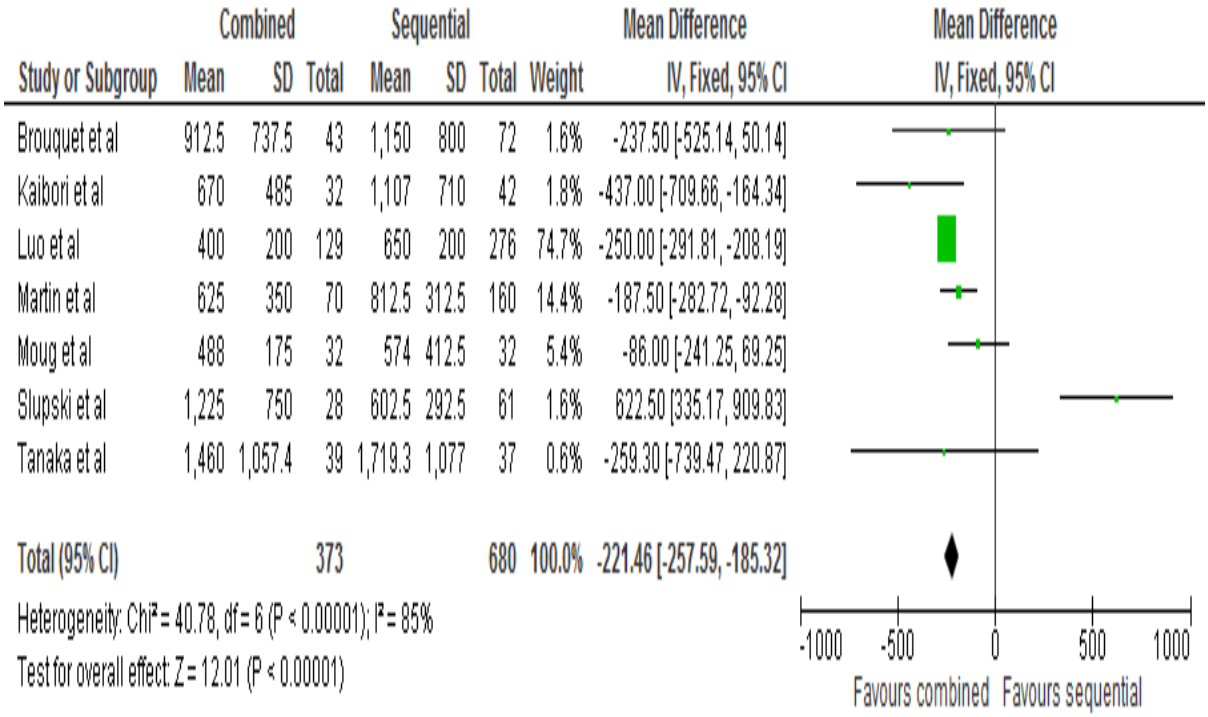
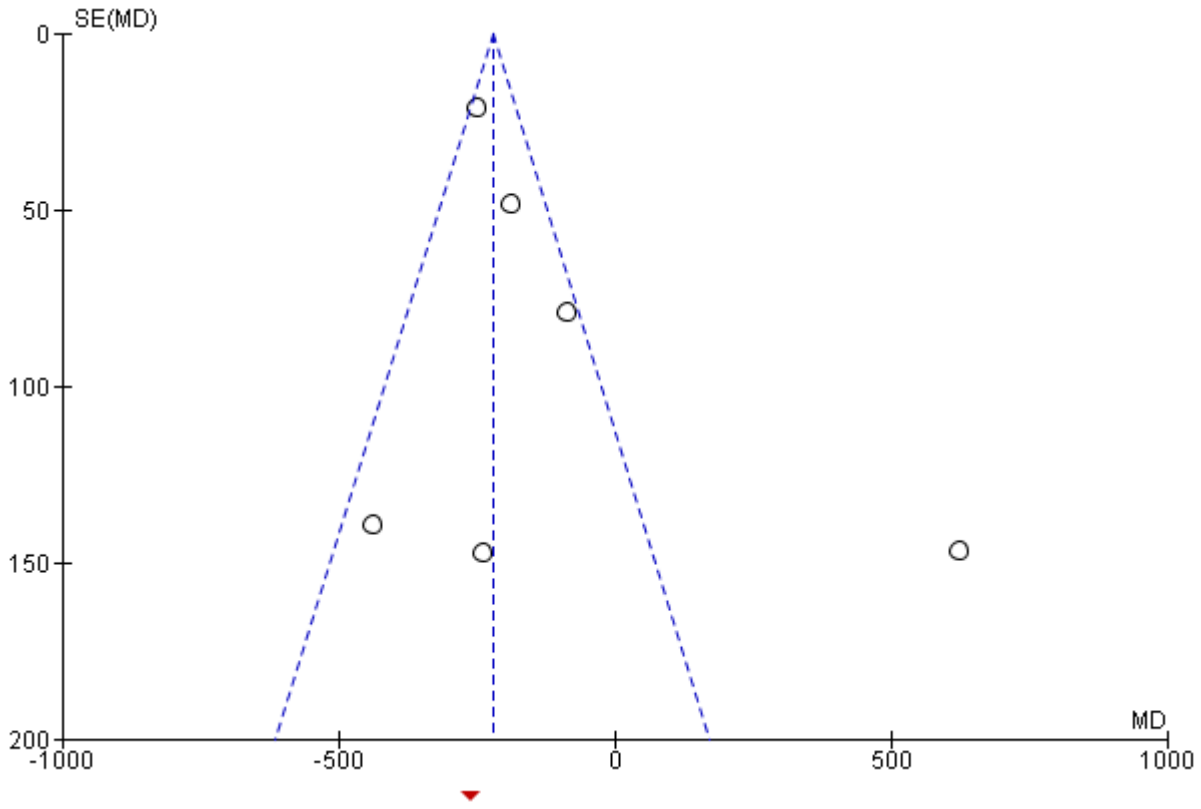


Figure 4.28: Overall meta-analysis - funnel plot for the outcome operative blood loss. One study,[172] which favoured the sequential resection group for this outcome, is well out of the 95% CI lines. There was no evidence of publication bias.



The number of patients requiring blood transfusion was reported by six studies.[162, 163, 170, 175, 181, 185] The total number of patients transfused for both procedures of the sequential resection group was used for comparison. There was no significant difference between the two groups (Figure 4.29; OR 1.29, 95% CI 0.93, 1.80; P=0.13), with no evidence of heterogeneity (P=0.36, I-square 8%) or publication bias for this outcome (Figure 4.30).

Figure 4.29: Overall meta-analysis - forest plot for the outcome number of patient requiring blood transfusion. There was no statistically significant difference in the proportion of patients transfused between the combined and sequential resection groups.

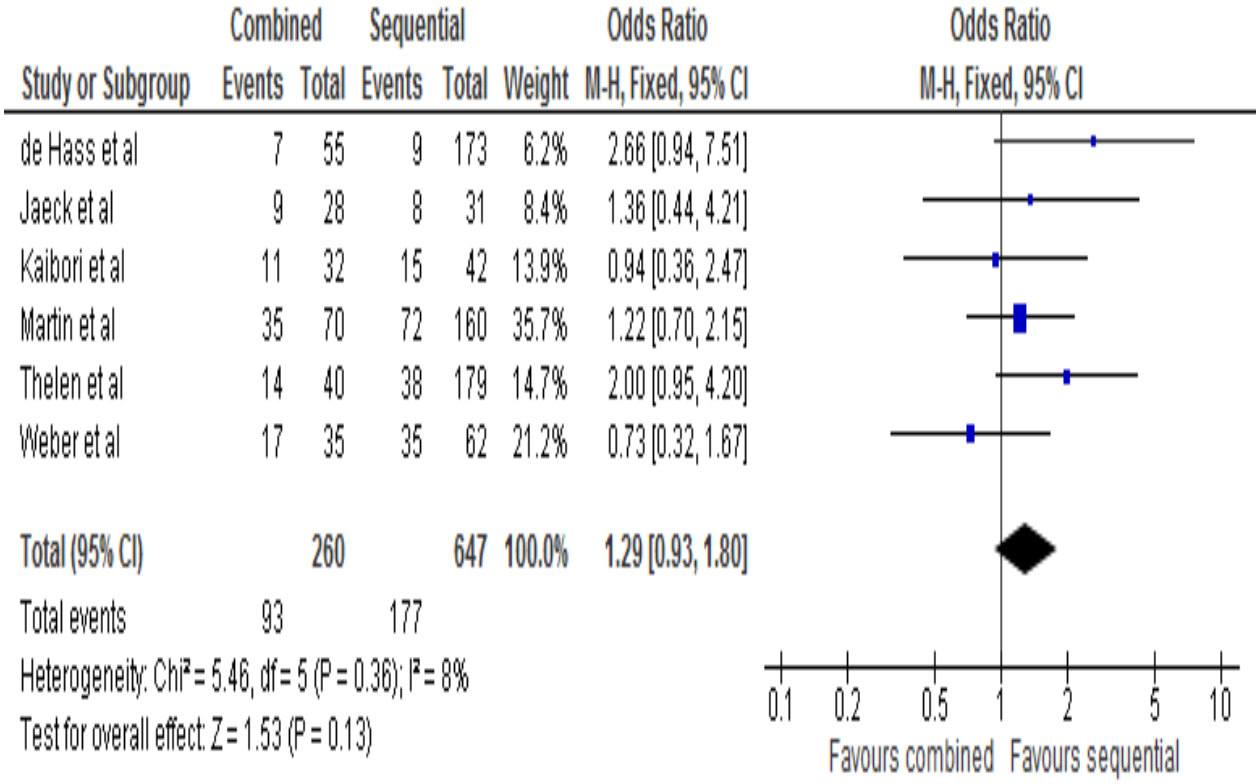
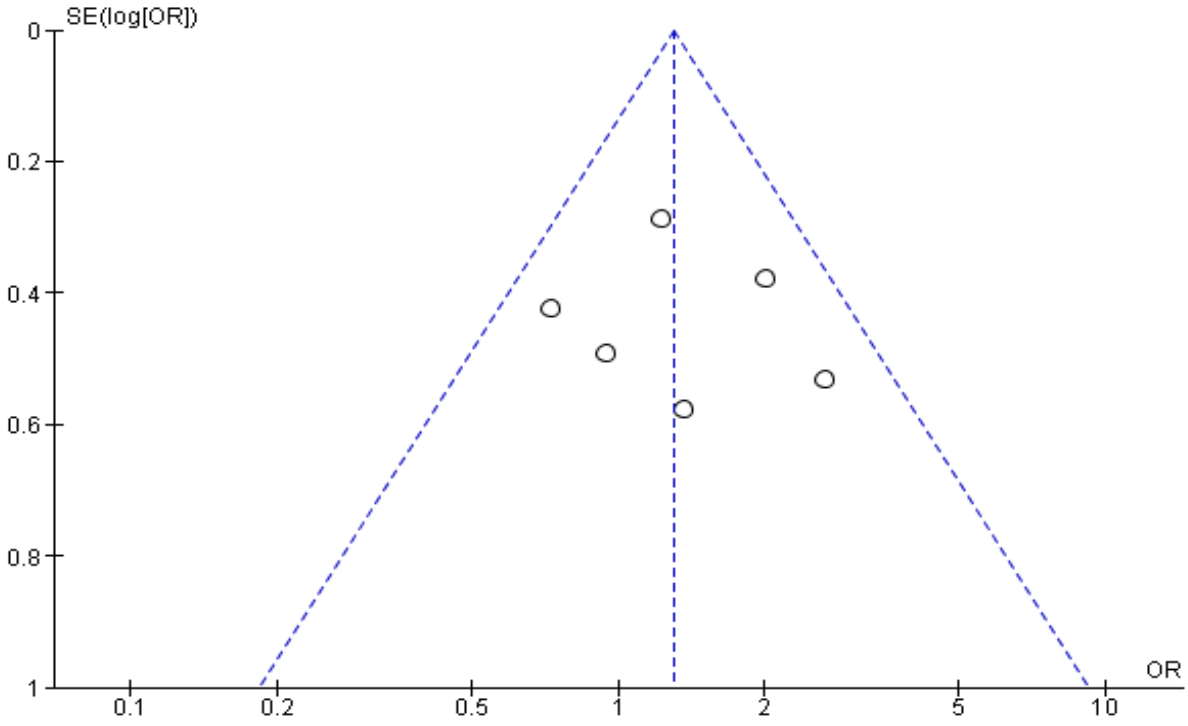


Figure 4.30: Overall meta-analysis - funnel plot for the outcome number of patient requiring blood transfusion. There was no evidence of publication bias.



Duration of hospital stay was reported by ten studies.[164-166, 170, 172, 174, 175, 177, 181, 182] The total length of hospital stay for both surgeries of the sequential resection group was used in the analysis. The combined resection group was found to have significantly shorter duration of hospital stay compared to the sequential resection group (Figure 4.31; MD -5.52 days, 95% CI -5.94, -5.10; P<0.001), with significant heterogeneity between studies (P<0.001, I-square 95%). There was evidence of publication bias as shown by the asymmetry of the funnel plot (Figure 4.32).

Figure 4.31: Overall meta-analysis - forest plot for the outcome duration of hospital stay. The combined resection group had significantly shorter duration of hospital stay compared to the sequential resection group, with significant heterogeneity identified.

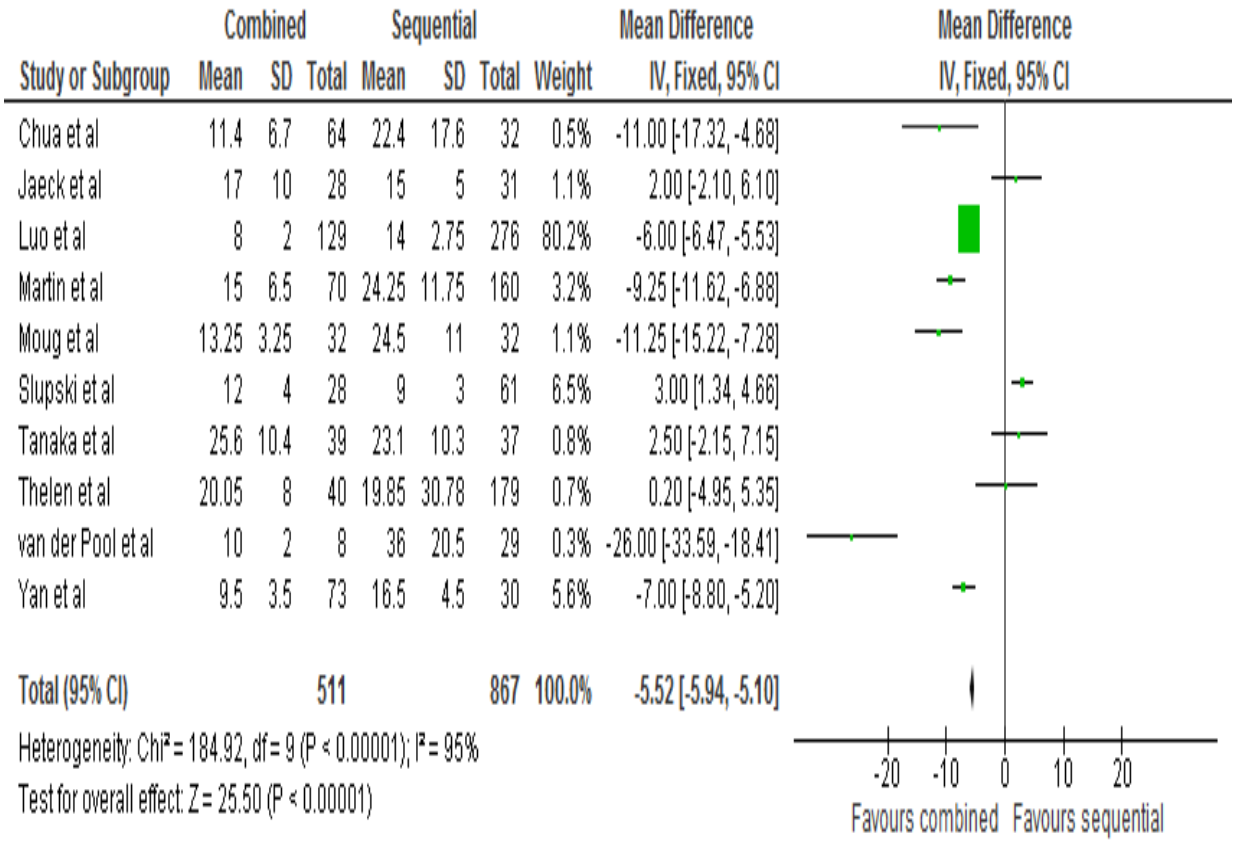
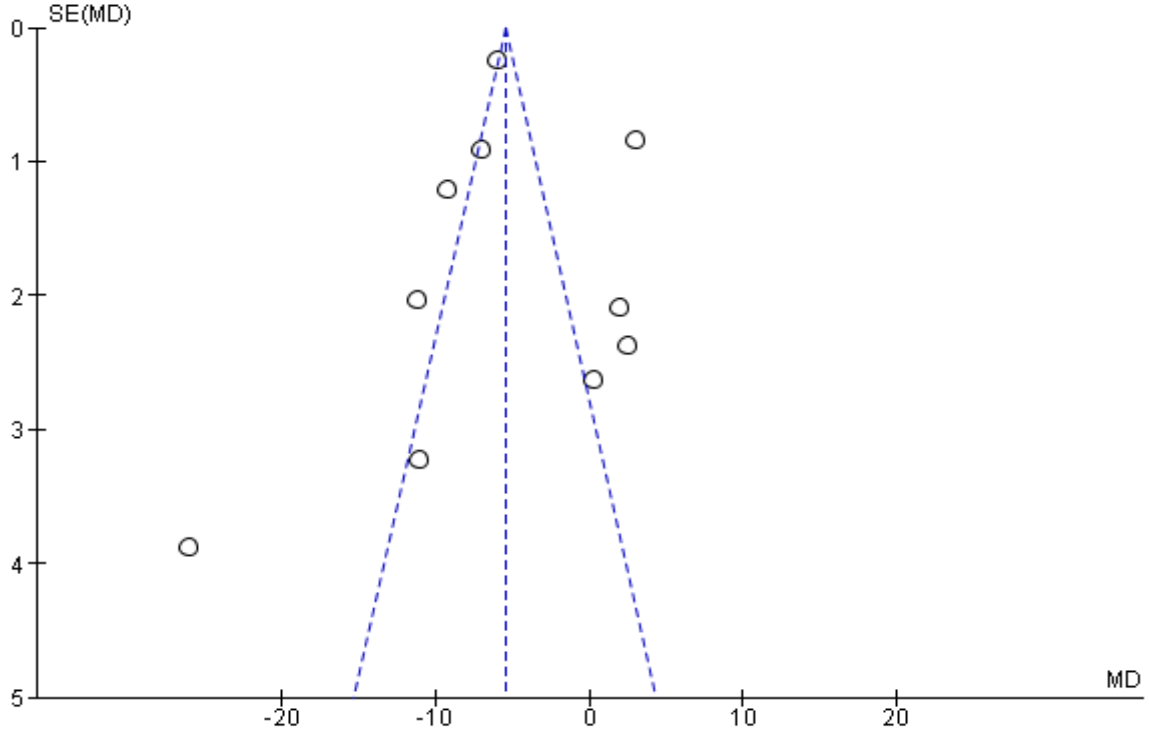


Figure 4.32: Overall meta-analysis - funnel plot for the outcome duration of hospital stay. There was evidence of publication bias based on the asymmetry of the funnel plot.



4.3.3.3. Overall survival and recurrence-free survival

The overall survival rate was reported by sixteen studies.[110, 112, 162, 172-179, 181-185] Meta-analysis with the random-effects model showed no significant difference in overall survival between the combined and the sequential resection groups (Figure 4.33; HR 1.00, 95% CI 0.86, 1.15; P=0.96); meta-analysis with the fixed-effect model showed the combined resection group to have significantly better overall survival rate compared to the sequential resection group (Figure 4.34; HR 0.95, 95% CI 0.92, 0.98; P=0.004). The reason for the difference between the two models was the significant heterogeneity between studies for this outcome (P<0.001, I-square 94%). The asymmetry of the funnel plot for this outcome also suggested evidence of publication bias (Figure 4.35). The random-effects model was preferred for the interpretation of this outcome because it takes into consideration the heterogeneity between studies and gives a more conservative effect estimate.

Figure 4.33: Overall meta-analysis - forest plot for the outcome overall survival using the random-effects model. There was no statistically significant difference in overall survival between combined and sequential procedure using the random-effects model.

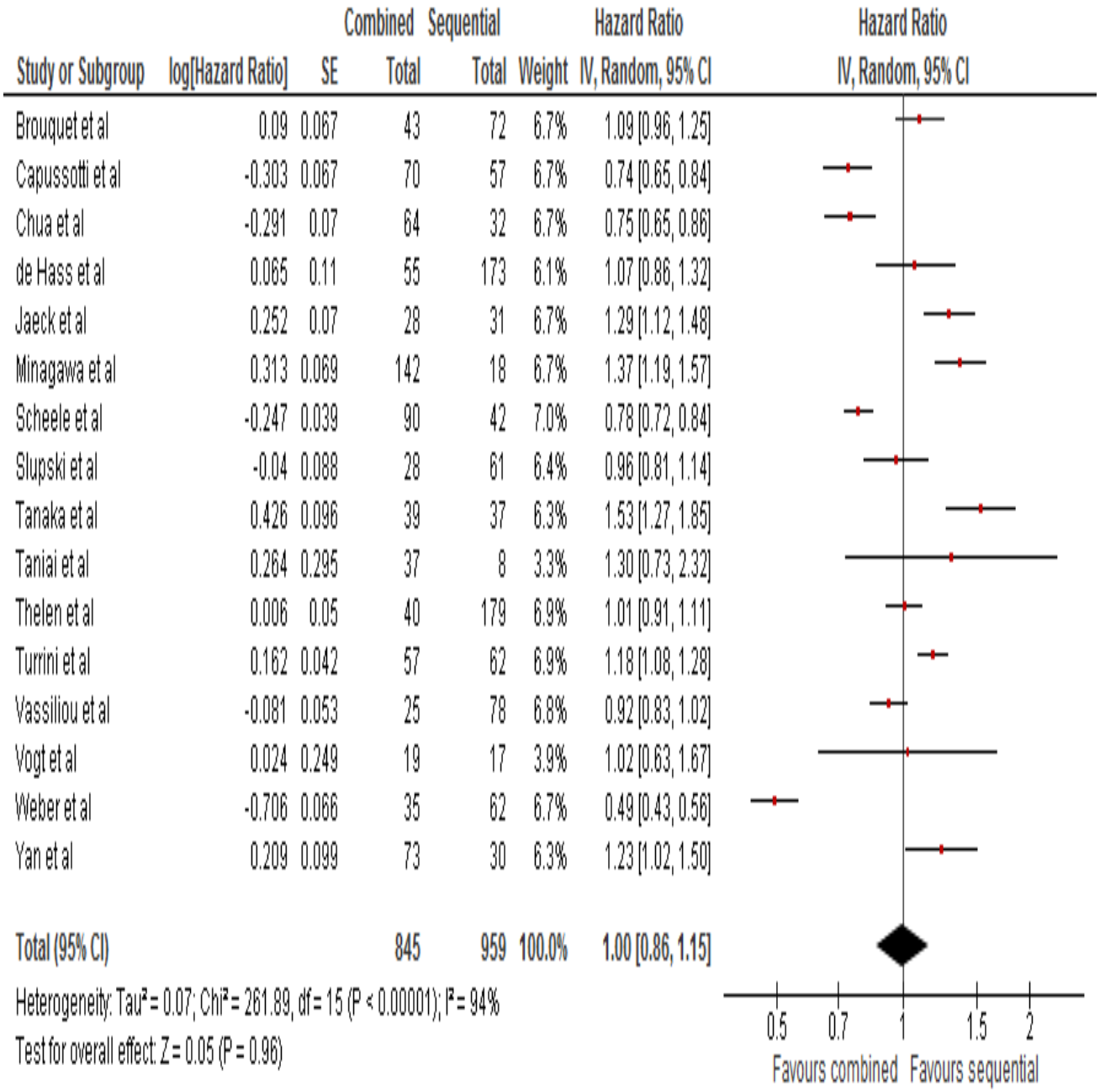


Figure 4.34: Overall meta-analysis - forest plot for the outcome overall survival using the fixed-effect model. The combined resection group had significantly better overall survival rate compared to the sequential resection group using the fixed-effect model.

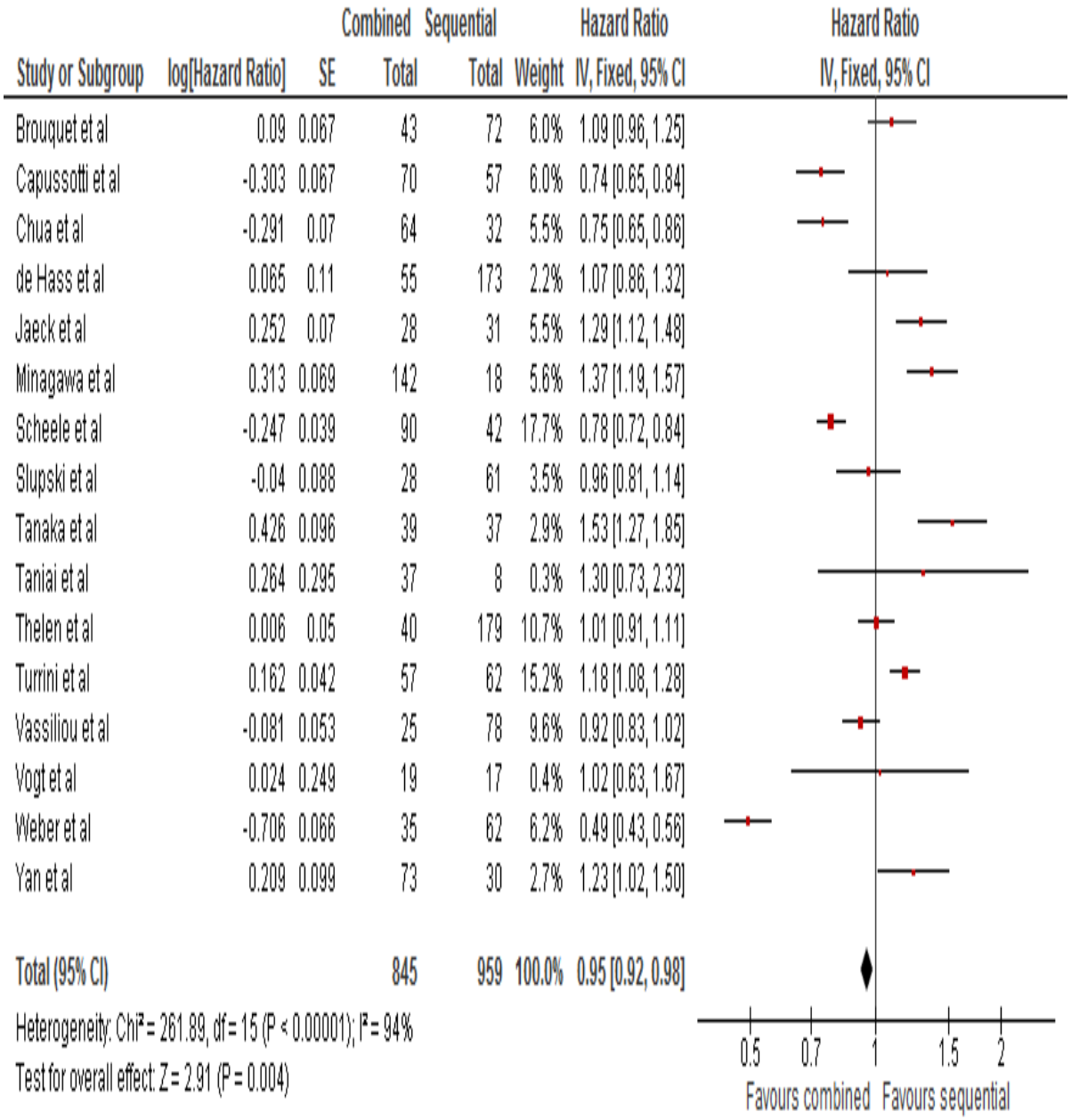
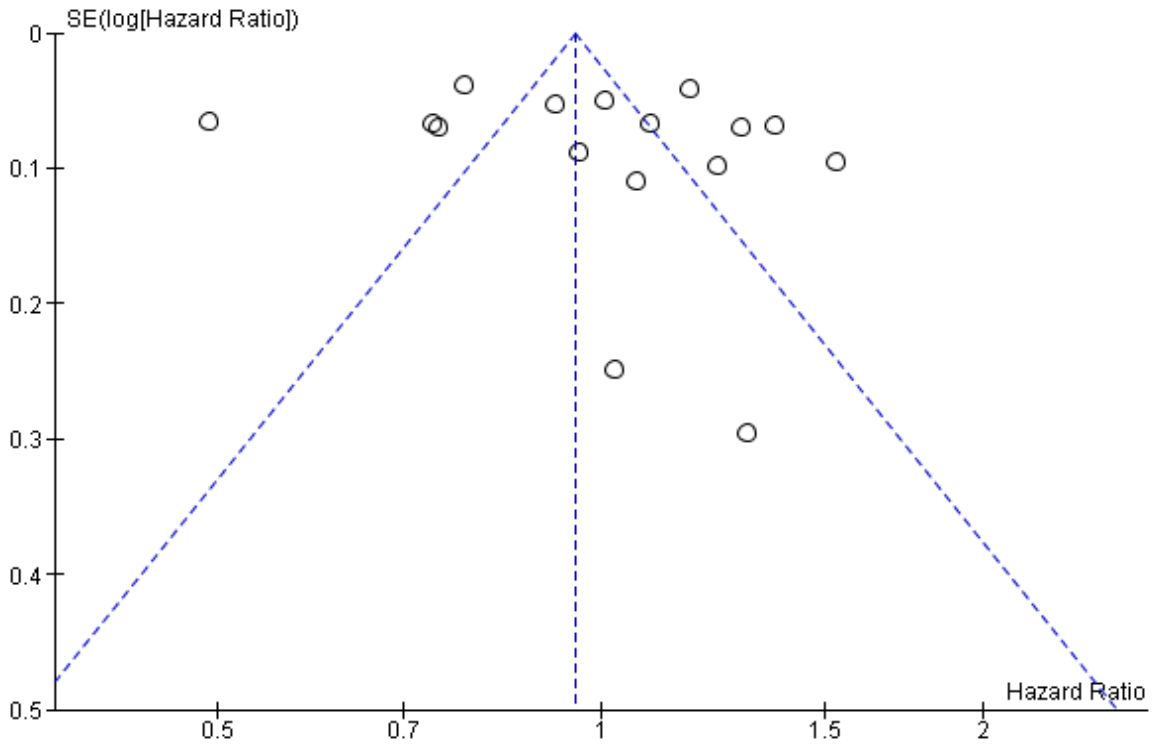


Figure 4.35: Overall meta-analysis - funnel plot for the outcome overall survival. The asymmetry of the funnel plot suggested evidence of publication bias.



Recurrence-free survival was reported by six studies.[163, 174, 177, 179, 180, 182] Meta-analysis using the random-effects model showed no significant difference in recurrence-free survival between the combined and the sequential resection groups (Figure 4.36; HR 0.85, 95% CI 0.71, 1.02; P=0.08); meta-analysis using the fixed-effect model showed the combined resection group to have significantly better disease free survival rate compared to the sequential resection group (Figure 4.37; HR 0.86, 95% CI 0.83, 0.90; P<0.001). There was significant heterogeneity between studies (P<0.001, I-square 91%) which explains the difference in outcomes between the two models. The random-effects model was used for the interpretation of this outcome due to its more conservative value. There was no significant evidence of publication bias (Figure 4.38). None of the included studies reported on quality of life.

Figure 4.36: Overall meta-analysis - forest plot for the outcome recurrence-free survival using the random-effects model. There was no statistically significant difference in recurrence-free survival between the combined and sequential procedures when using the random-effects model.

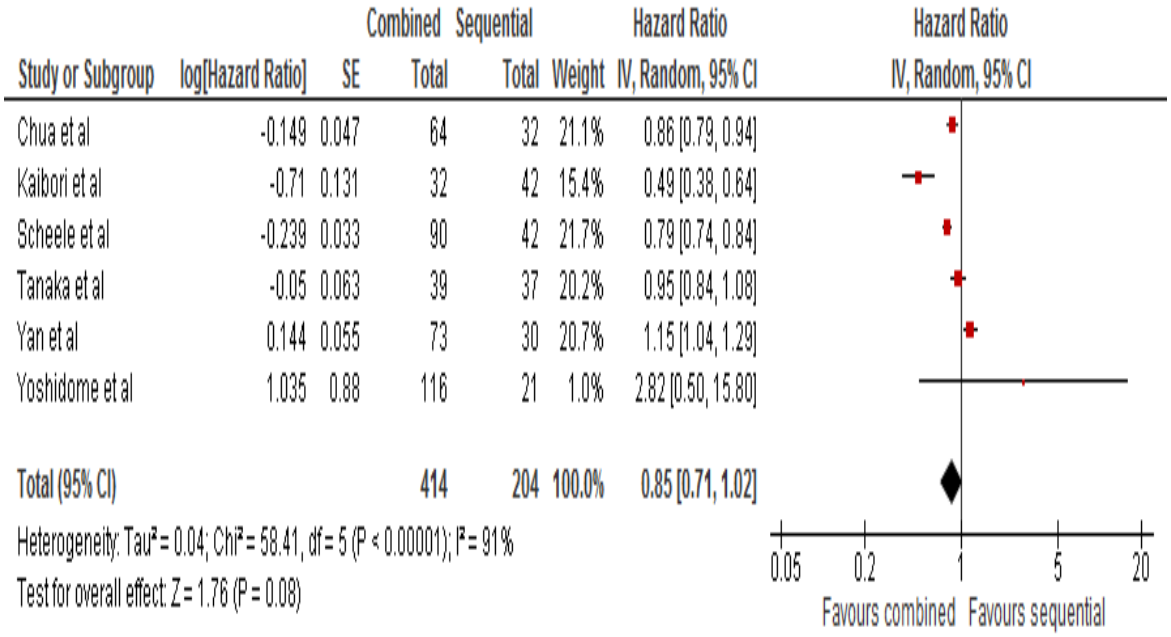


Figure 4.37: Overall meta-analysis - forest plot for the outcome recurrence-free survival using the fixed-effect model. The combined resection group was found to have significantly better disease free survival rate compared to the sequential resection group when using the fixed-effect model.

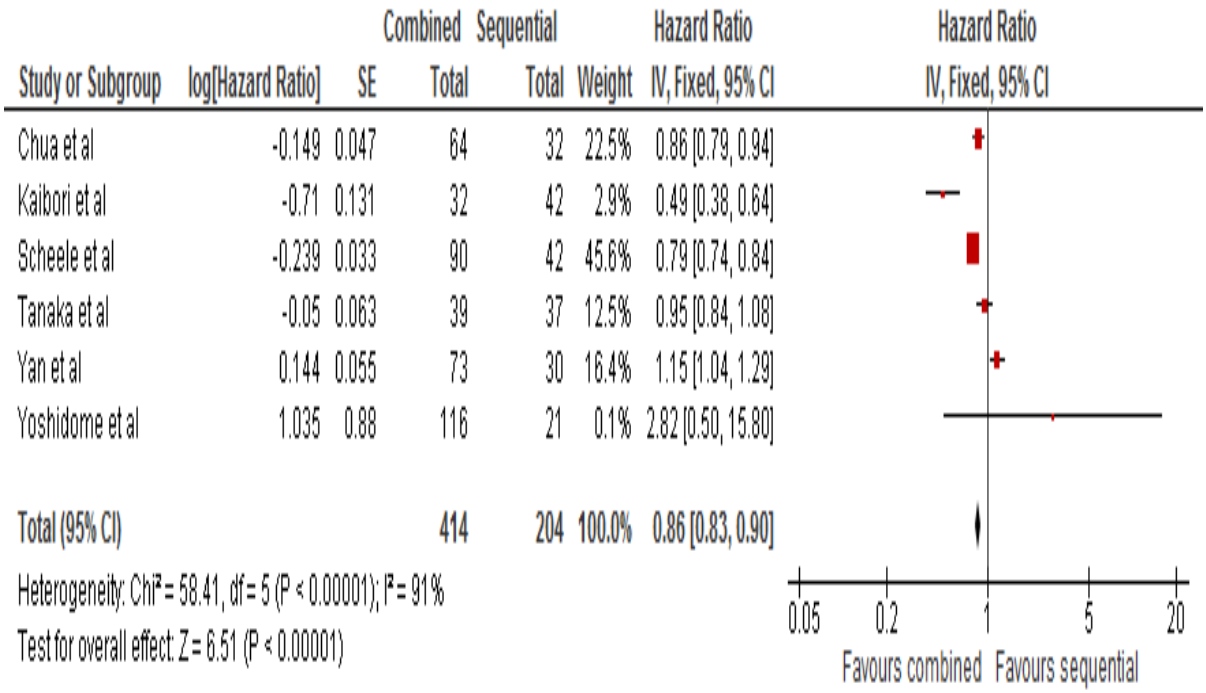
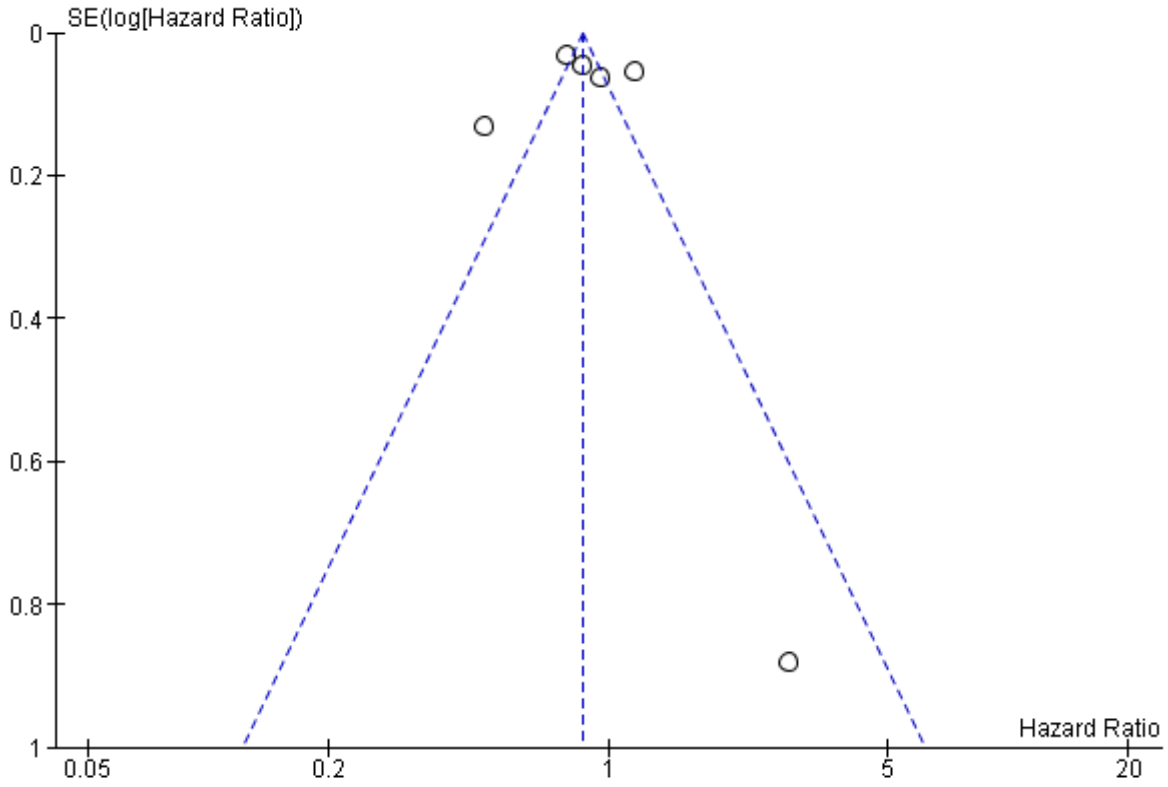


Figure 4.38: Overall meta-analysis - funnel plot for the outcome recurrence-free survival. There was no evidence of publication bias.



4.3.4 Sensitivity analysis

4.3.4.1. More recent studies

The only difference in the results of the sensitivity analysis including more recent studies compared to the results of the overall meta-analysis was regarding recurrence-free survival which was reported by only one study[163] in this sensitivity analysis, and this study reported better disease free survival in the combined resection group compared to the sequential resection group. All the other results of the sensitivity analysis of more recent studies were the same with the overall meta-analysis. Sensitivity analysis of the nine studies[112, 162-166, 170-172] published during or after 2009 demonstrated no significant difference between the combined and sequential resection groups in perioperative mortality (OR 0.92, 95% CI 0.31, 2.69; P=0.87), overall complications (OR 1.19, 95% CI 0.91, 1.56; P=0.20), hepatectomy related complications (OR 1.02, 95% CI 0.65, 1.60; P=0.93), general complications (OR 1.17, 95% CI 0.82, 1.69; P=0.39), proportion of patients transfused (OR 1.31, 95% CI 0.84, 2.04; P=0.23), and overall survival (HR 1.05, 95% CI 0.95, 1.15; P=0.33).

Similar to the overall meta-analysis, sensitivity analysis of more recent studies, found operative blood loss to be significantly less in the combined resection group during analysis with the fixed-effect model (MD -221.24 mL, 95% CI -257.48, -185.00; P<0.001), but the difference disappeared when the random-effects model was used for the analysis (MD -118.14 mL, 95% CI -277.44, 41.15; P=0.15). There was significant heterogeneity for operative blood loss (P<0.001, I-square 88%). Operating time was found to be significantly shorter in the combined resection group during analysis with the fixed-effect model (MD -55.49 min, 95% CI -68.89, -42.10; P<0.001), but the difference disappeared when the random-effects model was used for the analysis (MD -75.82 min, 95% CI -211.83, 60.18; P=0.27), and there was significant heterogeneity for this outcome (P<0.001, I-square 99%). The length of hospital stay was significantly shorter in the combined resection group compared to the sequential resection group (MD -5.61 days, 95% CI -6.05, -5.16; P<0.001), during analysis with both the fixed-effect and random-effects models, with significant heterogeneity between studies (P<0.001; I-square 97%).

4.3.4.2. Studies scoring 8 or more stars

The results of the sensitivity analysis of the studies which scored 8 or more stars on the modified NOS,[110, 112, 162, 163, 165, 173-177] were all similar to the overall meta-analysis, except for blood transfusion, where the sequential resection group was found to have significantly fewer patients transfused compared to the combined resection group (OR 1.69, 95% CI 1.01, 2.83; P=0.04), with no significant heterogeneity between studies (P=0.31, I-square 14%). Similar to the overall meta-analysis, this sensitivity analysis showed no significant difference between the combined and sequential resection groups in perioperative mortality (OR 2.24, 95% CI 0.82, 6.11; P=0.12), general complications (OR 0.86, 95% CI 0.55, 1.33; P=0.49), hepatectomy related complications (OR 0.68, 95% CI 0.38, 1.21; P=0.19), and overall survival (HR 0.99, 95% CI 0.95, 1.04; P=0.75).

The combined resection group was found to have significantly fewer overall complications compared to the sequential resection group when compared using the fixed-effect model (OR 0.72, 95% CI 0.54, 0.96; P=0.02), but no significant difference was found between the two groups when using the random-effects model (OR 0.72, 95% CI 0.50, 1.06; P=0.09). There was significant heterogeneity for overall complications (P=0.10, I-square 39%). Recurrence-free survival of the combined resection group was found to be significantly better during analysis with the fixed-effect model (HR 0.93, 95% CI 0.87, 0.99; P=0.03), but there was no significant difference with the random-effects model (HR 0.81, 95% CI 0.57, 1.14; P=0.22). There was significant heterogeneity for recurrence free survival (P<0.001, I-square 95%).

Similar to the overall meta-analysis, operating time was found to be significantly shorter in the combined resection group during analysis with the fixed-effect model (MD -42.50 min, 95% CI -57.52, -27.47; P<0.001), but the difference disappeared when the random-effects model was used for the analysis (MD -14.53 min, 95% CI -143.77, 114.70; P=0.83). There was significant heterogeneity for operating time (P<0.001, I-square 98%). Operative blood loss was found to be significantly less in the combined resection group during analysis with the fixed-effect model (MD -221.46 mL, 95% CI -257.59, -185.32; P<0.001), but the difference disappeared when the random-effects model was used for the analysis (MD -128.37 mL, 95% CI -279.28, 22.53; P=0.10), and there was significant heterogeneity for this outcome (P<0.001, I-square 85%). The length of hospital stay was significantly shorter in the combined resection group compared to the

sequential resection group (MD -7.22 days, 95% CI -8.74, -5.71; P<0.001), during analysis with both the fixed-effect and random-effects models, with significant heterogeneity between studies (P<0.001; I-square 78%).

4.3.4.3. Studies reporting on more than 60 resections in the combined resection group

Sensitivity analysis of the 9 studies[113, 164, 170, 173, 174, 177-180] reporting on more than 60 resections in the combined resection group, had similar results with the overall meta-analysis except for operative blood loss and operating time. Operative blood loss was found to be significantly reduced in the combined resection group compared to the sequential resection group (MD -239.90 mL, 95% CI -278.18, -201.62; P<0.001), during analysis with both the fixed-effect and random-effects models, with no significant heterogeneity between studies (P=0.24; I-square 28%). Operating time was found to be significantly shorter in the combined resection group compared to the sequential resection group (MD -141.45 min, 95% CI -159.50, -123.41; P<0.001), with significant heterogeneity between studies (P=0.02, I-square 81%).

Similar to the overall meta-analysis, no significant difference was demonstrated between the combined and the sequential resection groups in perioperative mortality (OR 1.40, 95% CI 0.54, 3.59; P=0.49), overall complications (OR 1.08, 95% CI 0.86, 1.36; P=0.50), hepatectomy related complications (OR 1.18, 95% CI 0.74, 1.87; P=0.49), and proportion of patients transfused (OR 1.22, 95% CI 0.70, 2.15; P=0.48). There was no significant difference between the two groups regarding the general complications (OR 1.32, 95% CI 0.88, 1.98; P=0.18), but there was significant heterogeneity between studies for this outcome (P=0.09, I-square 58%). The length of hospital stay was significantly shorter in the combined resection group compared to the sequential resection group (MD -6.20 days, 95% CI -6.65, -5.75; P<0.001), during analysis with both the fixed-effect and random-effects models, with significant heterogeneity between studies (P=0.02; I-square 70%).

Overall survival of the combined resection group was found to be significantly better during analysis with the fixed-effect model (HR 0.87, 95% CI 0.82, 0.91; P<0.001), but there was no significant difference with the random-effects model (HR 0.93, 95% CI

0.73, 1.19; P=0.58). There was significant heterogeneity for overall survival (P<0.001, I-square 95%). Regarding recurrence-free survival, the combined resection group was found to do significantly better during analysis with the fixed-effect model compared to the sequential resection group (HR 0.87, 95% CI 0.83, 0.91; P<0.001), but there was no significant difference between the two groups using the random-effects model for the analysis (HR 0.93, 95% CI 0.76, 1.16; P=0.53), and there was significant heterogeneity for this outcome (P<0.001, I-square 92%).

4.4 DISCUSSION

This review used meta-analytical techniques to compare combined versus sequential resection for synchronous CLM. Twenty-four non-randomised retrospective comparative studies were included in this meta-analysis. This meta-analysis found no significant difference between the combined and sequential resection groups in perioperative mortality and morbidity. Specifically, there was no significant difference between the two groups in overall complications, hepatectomy related complications, general complications, bile leak, bowel anastomotic leak, cardiovascular complications, and respiratory complications. Operative blood loss and perioperative blood transfusion are two of the most important factors affecting perioperative morbidity and mortality during liver resection,[45, 46, 64, 65] and the current meta-analysis found no significant difference between the two groups in operative blood loss, and proportion of patients requiring blood transfusion. The above results, would suggest that combined resection is at least as safe as sequential resection in selected cases, and did not increase the rate of postoperative complications. In addition, the combined resection group was found to have a significantly shorter length of hospital stay compared to the sequential resection group, and this has important financial implications. Finally, the current meta-analysis demonstrated that combined resection is associated with comparable survival rates and recurrence-free rates as sequential resection.

Similar to the other meta-analyses comparing combined to sequential resections for synchronous CLM,[186-189] one of the major findings of the current meta-analysis was the significant heterogeneity between studies for important outcomes of interest. This heterogeneity persisted during sensitivity analysis of subgroups of studies. Importantly, when heterogeneity was identified, the heterogeneity was in the direction of the effect rather than its magnitude. This is important because when there is heterogeneity in the direction of the effect, it means that the beneficial or harmful effect of the intervention is not consistent across all studies. Whereas, if there is heterogeneity in the magnitude of the effect, it means that all the studies consistently report that the intervention is beneficial or harmful, but there is variation in how beneficial or harmful the intervention is. The current meta-analysis demonstrated how heterogeneity can affect the overall results of a meta-analysis depending on the model used to perform the meta-analysis. In the current meta-analysis, the fixed effect model demonstrated significant benefit for the

combined resection group compared to the sequential resection group for important outcomes of interest, e.g. operating time, operative blood loss, overall survival rate, and recurrence-free survival rate. For the same outcomes, the random-effects model found no significant difference between the two groups.

A researcher should be aware of the benefits and limitations of the different models available to perform a meta-analysis, and should understand how to choose the correct one. Choosing the wrong model for a meta-analysis may result in completely different outcomes reported by the meta-analysis, thus resulting into making the wrong recommendations which may significantly affect the overall management and care of patients. The difference in results between the fixed-effect and the random-effects model was due to the significant heterogeneity between studies. If there was no significant heterogeneity between the studies, the results between the fixed-effect and random-effects models would have been similar. In the presence of heterogeneity, the CI of the meta-analysed measure of effect is wider when the random-effects model is used.[141] Therefore, the random-effects model provides a more conservative value, and when there was disagreement in the results between fixed-effect and random-effects models, the random-effects model was chosen for the interpretation of results in the presence of heterogeneity.

When statistical heterogeneity between studies is discovered, it is important to attempt to identify the source of heterogeneity. The studies included in the current meta-analysis were all non-randomised retrospective comparative studies. Retrospective studies have inherent biases, most important of which, is, selection bias. Comparison between combined and sequential resection groups identified significant difference between the two groups in the hepatic metastatic burden of the included patients. Specifically, the sequential resection group had significantly higher rate of bilobar distribution of the liver metastases, greater proportion of major liver resections needed to be performed, and larger size of liver metastases. These statistically significant differences were favouring the combined resection group, suggesting a selection bias towards a lower metastatic burden in the patients belonging in this group. This selection bias may have led to results that favoured the combined resection group.

Furthermore, although there was no significant difference between combined and sequential resection groups in the number of colonic primaries, there was significant

variation between studies in the location of the primary, with one study including only rectal primaries, other studies including more rectal primaries in the combined or the sequential resection group, and other studies including mainly colonic primaries for both groups. This may be a source of heterogeneity for the outcomes reported by the included studies because, for example, a right hemicolectomy is technically easier to perform with lower risk of complications compared to an anterior resection or an abdominoperineal resection. A sensitivity analysis could not have been performed to test this possible source of heterogeneity because the included studies did not report their results separately for colonic or rectal tumours, and only one study[166] included only rectal primaries. The heterogeneity between studies may have also resulted due to the other potentially confounding variables, such as demographic characteristics, patient selection criteria, interim treatments (e.g. type of chemotherapy), surgeon's experience, and surgical technique used for liver resection and/or colorectal resection.

Meta-analysis of non-randomised studies, is useful in the absence of RCTs, and together with identifying the source of heterogeneity between the included studies, it may guide further researchers toward properly informed randomisation in future studies. Importantly, selection criteria should be established for patients who may be suitable for combined resection, besides simply comparing the safety and efficacy of the two resection strategies.[189] In addition, only limited hepatic disease should be assessed in both groups to avoid any bias related to the disease severity.

After resection of the primary tumour, patients undergoing sequential resection, would typically undergo chemotherapy and would be monitored for a period of 2-3 months. Those patients who did not exhibit disease progression during this period, would progress to liver resection. This 'test of time' approach, or interval re-evaluation, is strongly advocated to observe the biological behaviour of the metastatic disease following primary tumour resection, in order to select patients who will benefit from hepatic resection, and to avoid unnecessary major operation in patients who develop distant or an increased number of metastases during this period.[190] This interval re-evaluation approach may have biased the results favouring the sequential resection group by selecting tumours with better prognosis for liver resection. On the other hand, the postoperative immunodeficiency following the primary resection in sequential resections has been suggested to increase the risk of liver metastatic growth.[162, 191]

Over the last few years, there has been a major change to practise which is the switch to laparoscopic approach to resect the primary disease. The laparoscopic approach allows chemotherapy shortly after the primary resection. Because of this, a trial comparing sequential laparoscopic bowel resection followed by open liver resection versus combined resection by open surgery will not be suitable. In this case, a RCT comparing laparoscopic bowel resection followed by laparoscopic liver resection versus combined laparoscopic resection of primary and hepatic disease will be more suitable. For this RCT, only limited hepatic disease amenable to laparoscopic resection should be assessed in both groups.

Neoadjuvant chemotherapy prior to hepatectomy may facilitate the resectability of the liver lesions and treat occult metastases, but it may also lead to hepatic parenchyma damage. There have been concerns that patients who undergo combined resection without neoadjuvant chemotherapy may have a higher recurrence rate (currently unproven), and that combined resections run the risk of leaving behind undetected occult micro-metastases in the remnant liver.[180] Whether combined resection results in increased disease recurrence due to undetected micro-metastases, which did not have time to grow and be detected, is questionable, since the metastatic disease is present in the liver for a long period before diagnosis. On the other hand, shorter hospital stay and faster recovery after combined resection, allows patients to commence adjuvant chemotherapy without delay as opposed to patients undergoing sequential resections.[176]

This meta-analysis, did not find a significant difference between combined and sequential resections with regard to overall survival and recurrence-free survival. Despite the limitations of this meta-analysis, it is still important, as it has confirmed that in the presence of limited hepatic disease, combined resection is safe and produces the same oncological outcomes as sequential resection for patients with synchronous CLM. Therefore, combined resection of synchronous CLM would be justifiable in the presence of limited hepatic disease based on the findings of the current meta-analysis. Nevertheless, in cases of a higher burden of metastatic liver disease, combined resection is not yet justifiable, until further trials are produced with more severe, but importantly comparable, hepatic disease burden between combined and sequential resections.

There have been previous systematic reviews on this topic, but they did not report on all the important outcomes of interest and they have missed important studies[112, 162-166]

which were published after the search date of those systematic reviews. One previous meta-analysis published in Chinese included 7 studies, and reported a significantly increased mortality rate for the combined resection group compared to the sequential resection group, but no difference in morbidity between the two groups.[192]

A systematic review published by Hillingso *et al.* in 2009 included 16 retrospective studies, and suggested a tendency towards a shorter hospital stay and lower morbidity in the combined resection group, lower perioperative mortality in the sequential resection group, and similar 5-year survival between the two groups.[187] Hillingso *et al.* did not proceed to perform a meta-analysis of the outcomes and odds ratios were not calculated because of the following reasons: no RCTs were identified; the studies were biased because the sequential procedure was significantly more often undertaken in patients with left-sided primary tumours and with larger, more numerous, bi-lobar metastases; significant statistical heterogeneity between studies was identified.[187] The study concluded that combined resections can be undertaken in selected patients, provided that surgeons specialized in colorectal and hepatobiliary surgery are available.[187]

A meta-analysis published by Chen *et al.* in 2011, included 14 studies and reported significant statistical heterogeneity between the studies.[186] Chen *et al.* demonstrated similar operating time and operative blood loss between the two groups, a shorter length of hospital stay and lower morbidity rate with the combined resection group, and similar 1-year, 3-year, and 5-year survival rates between the two groups using the OR as the effect estimate for survival.[186] The authors concluded that combined resection is safe and efficient in the treatment of patients with synchronous CLM and recommended caution in interpretation of the results of their study due to the heterogeneity detected.[186]

After the current meta-analysis was performed, two more meta-analyses were published on the same subject in 2013,[188, 189] and another meta-analysis in 2014.[193] In their meta-analysis published in 2013, Li *et al.* found statistical heterogeneity between studies, and demonstrated a shorter hospital stay and lower total complication rate with the combined resection group, and no significant difference between the two groups in perioperative mortality, operative blood loss, 1-year, 3-year and 5-year recurrence-free and overall survival rate.[188] The study concluded that there is evidence that combined resection is an acceptable and safe option with carefully selected conditions and recommended future RCTs to confirm this conclusion.[188]

The other meta-analysis published in 2013, by Yin *et al.*, showed statistical heterogeneity between studies and reported fewer postoperative complications in the combined group, and no difference between the two groups in perioperative mortality, overall survival, and recurrence-free survival (HR was the effect estimate for the latter two outcomes).[189] The authors concluded that combined resection is safe and efficient in the treatment of patients with synchronous CLM and commented that their findings have to be carefully interpreted due to the lower level of evidence and the existence of heterogeneity.[189]

Finally, the meta-analysis published in 2014 by Feng *et al.* included 22 retrospective studies and found the number of liver metastases to be a major confounding factor.[193] After correction of baseline imbalances, the meta-analysis demonstrated no significant difference in postoperative mortality, morbidity, overall and disease-free survival between the two groups.[193] The study concluded that without baseline imbalances between the combined and sequential resection groups, the combined group had no statistical significant advantage in safety and efficacy.[193]

4.5 CONCLUSIONS

This meta-analysis demonstrated that combined resection for synchronous CLM is associated with comparable perioperative mortality and morbidity, operative blood loss, and blood transfusion requirements as sequential resection. It also demonstrated that the length of hospital stay is significantly reduced in patients after combined resection. Survival rates and recurrence-free rates were found to be similar between the two groups. However, the findings of this meta-analysis are limited by significant differences in metastatic disease severity between the two groups, the retrospective nature of the included studies, and the heterogeneity identified between studies. Therefore, this data should be used to justify a well-designed RCT with appropriate selection criteria comparing combined versus sequential resection in patients with comparable metastatic disease severity, and with both primary and hepatic disease amenable to laparoscopic resection.

CHAPTER 5

PAIRWISE META-ANALYSIS COMPARING THE SURVIVAL OF NODE POSITIVE VERSUS NODE NEGATIVE DISEASE AFTER HEPATECTOMY FOR COLORECTAL LIVER METASTASES

5.1 INTRODUCTION

The liver produces a large amount of lymph, which is estimated to be 25 to 50 % of the lymph flowing through the thoracic duct.[194] The hepatic lymph primarily comes from the hepatic sinusoids, and the hepatic lymphatic vessels fall into three categories depending on their locations: portal, sublobular, and superficial lymphatic vessels.[194] The portal lymphatic vessels are the most important with more than 80% of the hepatic lymph draining into them, while the remainder lymph drains through the sublobular and capsular lymphatic vessels.[194] Lymphatic vessels are abundant in the immediate vicinity of liver metastases,[194] and it is thought that lymphatic dissemination from hepatic metastases is the mechanism of tumour spread to extrahepatic lymph nodes.[195-197] Lymph node involvement in patients with CLM is believed to constitute a tertiary lymphatic metastasis or a 'metastasis of a metastasis'.[195, 196, 198]

Liver resection for CLM in the presence of hepatic lymph node involvement is controversial. Involvement of hepatic lymph nodes during liver resection is considered as a poor prognostic factor[114-116] and has been labelled as a contraindication to surgery.[115] The 5-year survival rate after liver resection in the presence of hepatic lymph node involvement varies between 0 and 4.3%.[117, 118, 199]

Macroscopic positive lymph node involvement may be evident preoperatively by radiological imaging or intraoperatively by identifying enlarged, firm, irregular lymph nodes, with obvious tumour infiltration. Also, positive lymph node involvement may be identified microscopically by examining the histology of the resected lymph nodes. Both macroscopic and microscopic lymph node involvement have been shown to have a negative impact on survival.[116-119] In about 14% to 15% of lymph nodes draining the liver considered uninvolved macroscopically, when examined closer histologically, they were found microscopically to be infiltrated by cancer cells.[117, 118]

The position of the positive lymph nodes has been suggested to affect prognosis. Patients who have involvement of common hepatic artery nodes and coeliac artery nodes (considered as group 2 nodes)[73, 200] have been reported to have a poorer prognosis than patients with involvement of the hepatoduodenal or retropancreatic group of nodes (considered as group 1 nodes).[73, 200] Approximately half of the microscopic disease is in

the hepatoduodenal and the retro-pancreatic group, which may be amenable to radical lymphadenectomy.[73, 200]

Hepatic node involvement detected pre-operatively or during surgery is generally considered a contraindication to hepatectomy for CLM. After adjusting for different factors such as tumour number,[117, 199, 201, 202] size,[117, 201, 202] distribution,[117, 202] and surgical resection margin,[201] survival rates for people with positive lymph nodes after hepatectomy, are similar to those in patients with unresectable CLM who underwent hepatic infusion chemotherapy,[200, 203, 204] suggesting that there is no benefit to these patients undergoing the mortality risk and morbidity associated with major liver surgery.

A Cochrane review published in 2010 aiming to compare curative liver resection with lymphadenectomy versus other treatments, concluded that there was no evidence in the literature to assess the role of surgery (liver resection alone or in combination with radiofrequency ablation or cryoablation) versus other treatments (neo-adjuvant chemotherapy, chemotherapy, or radiofrequency ablation) for patients with CLM with hepatic node involvement.[205] A systematic review published in 2008 assessed the role of lymphadenectomy during liver resection for CLM and concluded that here was no evidence of survival benefit for routine or selective lymphadenectomy.[200] The review also found that the survival rates were low in patients with positive lymph nodes draining the liver irrespective of whether they were detected by routine lymphadenectomy or by macroscopic involvement.[200] A case series by Carpizo *et al.* of patients undergoing liver resection for CLM with concomitant resection of extrahepatic disease, demonstrated that patients with hepatic portal lymph node metastases had worse survival than those with lung or ovarian metastases from colorectal cancer.[206]

On the other hand, other studies have shown that long-term survival can be achieved in highly selected patients undergoing liver resection along with resection of hepatic lymph node metastases. Adam *et al.* reported a 5-year disease-free survival rate of 11% and a 5-year overall survival rate of 18% after combined liver resection and lymphadenectomy in a cohort of patients with CLM who had preoperatively diagnosed hepatic lymph node involvement and had responded to neoadjuvant chemotherapy.[28] The same study also showed a difference in survival depending on the site of nodal metastases: the 5-year survival rate for patients who had metastases in the hepatic

pedicle lymph nodes and underwent hepatectomy and lymphadenectomy was better (25%) than for those undergoing hepatectomy along with resection of involved coeliac and para-aortic lymph nodes (0%).[28] Pulitano *et al.* evaluated the long-term outcomes of patients undergoing liver resection for CLM in the presence of extrahepatic disease, and found an overall 5-year survival rate of 18% in patients with lymph node involvement, most of whom had received preoperative as well as adjuvant chemotherapy.[207] Jaeck *et al.* reported a 3-year survival rate of 38% in patients who had nodal involvement in the hepatoduodenal ligament compared with 0% in patients who had nodal involvement around the hepatic artery and coeliac trunk.[117] Lymph node involvement in this study was diagnosed after routine lymphadenectomy, and the study demonstrated no survival advantage with routine lymphadenectomy.[117]

With significant improvements in perioperative cross sectional imaging, patient selection for resection, the safety of surgical techniques and chemotherapeutic agents in recent years, the previous contraindication to surgery in patients with hepatic node involvement is being challenged. Chemotherapy regiments have significantly improved over the years for the treatment of CLM. Adjuvant or neoadjuvant chemotherapy may play a role in patients undergoing resection where positive lymph nodes have been identified macroscopically preoperatively or during surgery, or microscopically on histology postoperatively.

There is a potential advantage in performing routine hepatic lymphadenectomy at the time of hepatectomy for CLM by removing microscopically involved lymph nodes and providing adjuvant chemotherapy in patients who do not have other poor prognostic factors. With more effective chemotherapy regimens, routine hepatic lymphadenectomy concurrent with liver resection for CLM could have a role in improving staging to guide adjuvant chemotherapy regimens.[119, 208] However, there have been no studies comparing hepatectomy alone with hepatectomy along with routine lymphadenectomy, and there is no consensus on whether routine hepatic lymphadenectomy or node sampling should be performed.[119, 208]

5.1.1. Aims of this review

The aims of this systematic review and meta-analysis are:

1. Determine the prognostic significance of hepatic lymph node status in patients undergoing hepatectomy for CLM by comparing survival and disease recurrence of patients with node positive versus node negative disease using meta-analytical techniques.
2. Investigate whether survival of patients with nodal involvement is improved by lymphadenectomy and if the extent of lymphadenectomy affects prognosis.
3. Investigate whether there might be a survival benefit from routine hepatic lymphadenectomy.
4. Determine whether hepatectomy is indicated in patients with proven macroscopic nodal involvement.

5.2 METHODS

5.2.1 Search strategy

The following databases were searched: MEDLINE from PubMed (January 1990 to November 2012), EMBASE (January 1990 to November 2012), and CENTRAL in The Cochrane Library (issue 1, 2012 from 1990). The following search strategy was used in MEDLINE: ("Neoplasm Metastasis"[MeSH] OR metasta* OR secondar* OR spread OR cancer OR carcinoma OR tumour OR tumor OR neoplasm) AND (colon OR colonic OR colorect* OR rectal OR rectum OR gut OR intestine OR bowel OR "Intestine, Large"[MeSH] OR "Colorectal Surgery"[MeSH] OR "Intestinal Neoplasms"[MeSH]) AND (("Liver"[MeSH] OR "Liver Neoplasms"[MeSH] OR "Liver Diseases"[MeSH] OR liver OR hepatic) AND (segmentectomy OR resection) OR "Hepatectomy"[MeSH]) AND "humans"[MeSH Terms] AND English[Lang] AND ("1990"[PDAT] : "3000"[PDAT]). Equivalent search strategies were used in EMBASE and CENTRAL.

5.2.2 Inclusion and exclusion criteria

The inclusion criteria for studies were as follows:

1. RCTs or comparative series
2. Published in journals from January 1990 onwards
3. Full text in English language
4. Clearly reported on hepatectomy for CLM
5. Clearly reported on the hepatic lymph node status
6. Reported survival or cancer recurrence data
7. Had a minimum duration of follow-up of 1 year

The exclusion criteria for studies were as follows:

1. Included liver resection for cancers other than CLM (primary or secondary)
2. Included repeat or multistage liver resections
3. Reported on combined excision of liver and lung metastases

4. Less than 10 patients underwent hepatectomy
5. Hepatic lymph node status was not clearly reported
6. Mentioned extrahepatic disease but not clearly stated as involving hepatic lymph nodes
7. Mentioned regional lymph nodes but not clearly stated whether the lymph nodes drain the primary tumour or the metastases
8. Not possible to identify the survival or recurrence data for hilar node positive and negative status separately
9. No controls reported (i.e. survival reported only in node negative and node positive patients who did not undergo hepatectomy)
10. More than 10 % of patients lost to follow-up

5.2.3 Data extraction

The following data were independently extracted by two review authors (Constantinos Simillis and Michael Jacovides) from each study using a custom-designed data extraction form: first author, language of publication, country and year(s) of conduct of the study, year of publication, type of study, sample size, participant characteristics (such as age, sex, underlying disease, comorbidities), study design, inclusion and exclusion criteria used in individual studies, length of follow up, patients lost to follow-up, tests performed during follow-up period, any adjuvant or neoadjuvant therapy given, indications for chemotherapy, hepatic lymph node involvement and how it was diagnosed (microscopic or macroscopic or both), whether routine or selective hepatic lymphadenectomy was performed, group of nodes dissected, survival and mortality data, time to recurrence data, type of recurrence (including local or regional or remote in relation to liver and the actual sites of recurrence). Any discrepancies between the two reviewers were resolved through discussion.

5.2.4 Risk of bias

The risk of bias of the included trials was assessed based on the following bias risk domains: allocation sequence generation, allocation concealment, blinding of

participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and vested interest bias. These bias risk domains were chosen based on the advice of The Cochrane Collaboration,[141] and the Cochrane Hepato-Biliary Group Module.[209] For each of these risk domains of bias the studies were categorized as low risk, uncertain risk, and high risk of bias. A trial was considered at low risk of bias if the trial was assessed as at low risk of bias for all domains. Trials with uncertain risk of bias or with high risk of bias for one or more domains were considered trials with high risk of bias.

In detail, the risk of bias of the included trials was assessed for the following domains:[210-216]

Allocation sequence generation

• Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent adjudicator.

• Uncertain risk of bias: the trial was described as randomised, but the method of sequence generation was not specified.

• High risk of bias: the sequence generation method was not, or may not have been, random. This includes quasi-randomised studies, i.e. those studies using dates, names, or admittance numbers to allocate participants.

Allocation concealment

• Low risk of bias: allocation was controlled by a central and independent randomisation unit, sequentially numbered, opaque and sealed envelopes, or something similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.

• Uncertain risk of bias: the trial was described as randomised, but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.

• High risk of bias: if the allocation sequence was known to the investigators who assigned participants or the study was quasi-randomised.

Blinding of participants and personnel

• Low risk of bias: blinding was performed adequately, or the outcome measurement was not likely to be influenced by lack of blinding.

• Uncertain risk of bias: information was insufficient to allow assessment of whether the type of blinding used was likely to induce bias on the estimate of effect.

• High risk of bias: no blinding or incomplete blinding and the outcome or the outcome measurements were likely to be influenced by lack of blinding.

Blinding of outcome assessors

• Low risk of bias: blinding was performed adequately, or the outcome measurement was not likely to be influenced by lack of blinding.

• Uncertain risk of bias: information was insufficient to allow assessment of whether the type of blinding used was likely to induce bias on the estimate of effect.

• High risk of bias: no blinding or incomplete blinding and the outcome or the outcome measurements were likely to be influenced by lack of blinding.

Incomplete outcome data

• Low risk of bias: the underlying reasons for missing data were unlikely to make treatment effects depart from plausible values, or proper methods have been employed to handle missing data.

• Uncertain risk of bias: information was insufficient to allow assessment of whether the missing data mechanism in combination with the method used to handle missing data was likely to induce bias on the estimate of effect.

• High risk of bias: the crude estimate of effects (e.g., complete case estimate) was clearly biased because of the underlying reasons for missing data, and the methods used to handle missing data were unsatisfactory.

Selective outcome reporting

• Low risk of bias: pre-defined or clinically relevant and reasonably expected outcomes were reported.

• Uncertain risk of bias: not all pre-defined or clinically relevant and reasonably expected outcomes were reported, or they were not reported fully, or it was unclear whether data on these outcomes were recorded.

• High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported; data on these outcomes were likely to have been recorded.

Vested interest bias

• Low risk of bias: the trial was conducted by a party with no vested interests (i.e., a party benefiting from the results of the trial) in the outcome of the trial.

• Uncertain risk of bias: It was not clear if the trial was conducted by a party with vested interest in the outcome of the trial.

• High risk of bias: the trial was conducted by a party with vested interests in the outcome of the trial (such as a drug manufacturer).

5.2.5 Outcomes of interest and definitions

The following outcomes were used to compare patients found to have positive lymph nodes versus patients with negative lymph nodes:

1. Survival at 1 year postoperatively
2. Survival at 3 years postoperatively
3. Survival at 5 years postoperatively
4. Overall survival expressed as time-to-event outcome

The following definitions were used in this meta-analysis:

- *Hepatic lymph nodes:* The term 'hepatic' has been used to maintain consistency and includes all subgroups of hepatic regional lymph nodes. The different terms used by different authors to define subgroups were as follows: hilar nodes, portal nodes, hepatoduodenal ligament nodes, hepatic pedicle nodes (nodes along the hepatoduodenal ligament, retropancreatic, common hepatic artery and celiac artery), perihepatic nodes, retropancreatic nodes, pedicular nodes (distal to gastroduodenal artery branch), common hepatic artery nodes, celiac nodes, para-aortic nodes and regional nodes.
- *Primary site*: Primary site of origin in the colon or rectum
- *Local recurrence in liver:* Recurrence at the site of liver resection. This has no relation to the recurrence of the tumour at the primary site.
- *Regional nodal recurrence:* Perihepatic area including porta hepatis. Again, this has no relation to the regional lymph nodes draining the primary tumour site.

- *Remote recurrence:* Recurrence of cancer in sites not included in the above two categories. In most cases (except in hepatic flexure tumours), recurrence at the primary site will be included in this category.
- *Macroscopic lymph node involvement:* Lymph node involvement as detected radiologically (preoperatively or perioperatively) or by visual and tactile assessment.
- *Microscopic lymph node involvement:* Lymph node involvement not detected radiologically or by visual and tactile assessment, but detected by microscopic examination of resected lymph nodes.
- *Lymph node involvement:* Macroscopic or microscopic lymph node involvement or both.
- *No lymph node involvement:* Neither macroscopic nor microscopic lymph node involvement.
- *Routine lymphadenectomy:* Lymphadenectomy (of nodes draining the liver) performed routinely in the presence or absence of lymph node involvement.

5.2.6 Statistical analysis

For detailed explanation of the statistical analysis please refer to section 2.3.4. Analysis was conducted using Review Manager Version 5.1.[138]

Statistical analysis of the binary outcomes (1-year, 3-year, and 5-year survival) was performed using the OR and was reported with 95% CI.[140] The MH method was used to combine the OR for these outcomes. OR represents the odds of a patient surviving in the positive lymph node group of patients compared to the negative lymph node group of patients at 1 year, 3 years, and 5 years. An OR of less than one favoured patients with negative lymph nodes.

The HR was used to compare the time-to-event outcome ‘overall survival’ between the lymph node positive and lymph node negative groups of patients. The generic inverse variance method was used to combine the time-to event outcomes. An HR of less than one favoured the negative lymph node group.

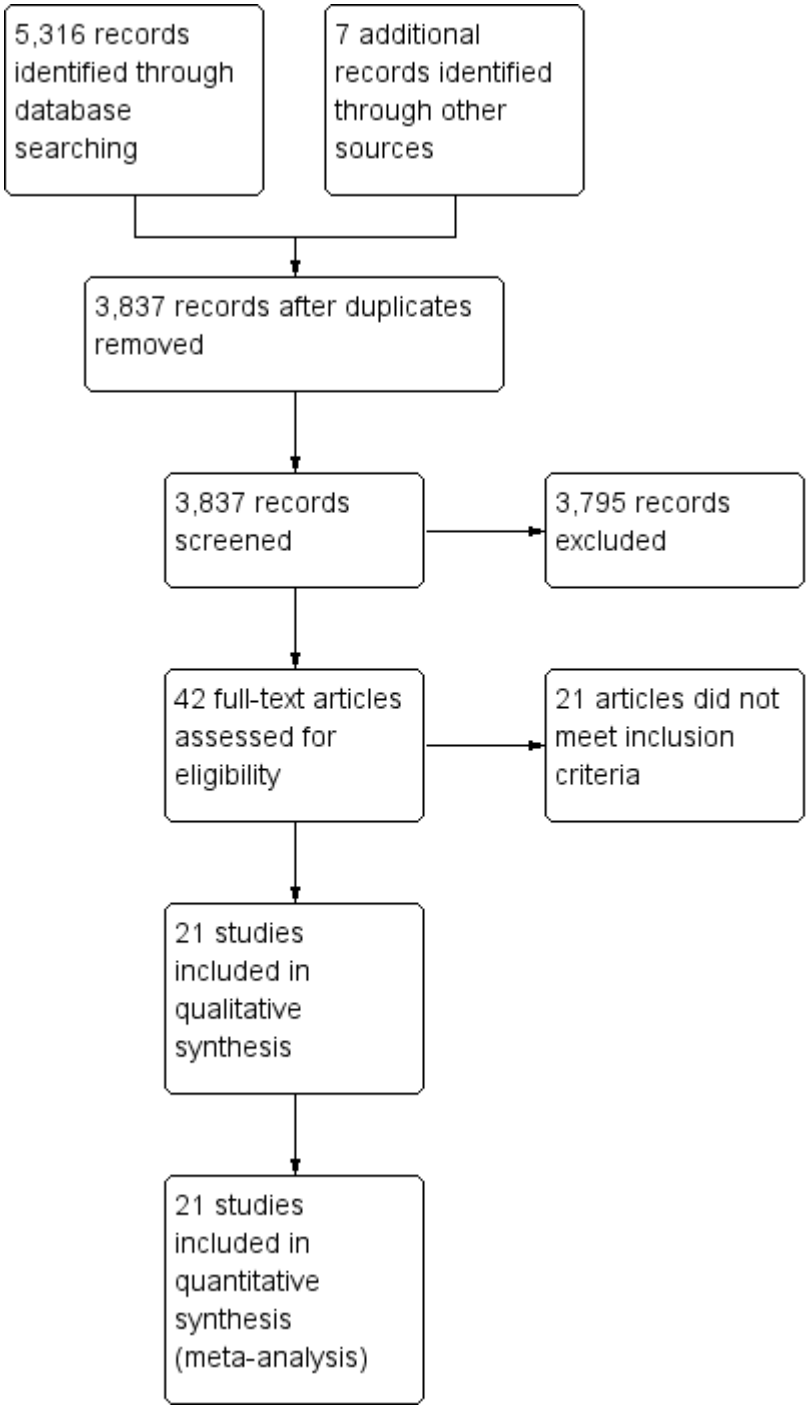
Heterogeneity was explored using the chi-squared test, with significance set at the P<0.10 level, and the amount of heterogeneity was determined by means of I-square. Three further strategies were used to quantitatively assess heterogeneity. First, graphical exploration with funnel plots was used to evaluate publication bias.[145, 147] Second, data was analysed using both random-effects and fixed-effect models. Where there was no difference between the results of random-effects and fixed-effect models that would change interpretation of the results, the results of the fixed-effect model were reported; otherwise, both the results were reported. Third, sensitivity analysis was undertaken based on the following factors: whether the studies included nodes involved macroscopically or microscopically, whether routine lymphadenectomy or selective lymphadenectomy was performed, whether chemotherapy was used, and whether only the lymph nodes along the hepatoduodenal ligament were removed (as compared with the removal of the other groups of nodes).

5.3 RESULTS

5.3.1 Eligible studies

A total of 5,316 references were identified following the search strategy described above. Seven more references were identified for further assessment through scanning reference lists of the identified studies. The duplicates excluded between databases were 1,486. A further 3,795 clearly irrelevant references were excluded through screening titles and reading abstracts. The remaining 42 studies were reviewed in detail, and 21 of them were excluded because they did not meet the inclusion criteria. In total, 21 studies[28, 117-119, 197, 199, 201, 206-208, 217-227] met the inclusion criteria and were included in the meta-analysis. This is summarised in the study flow diagram in Figure 5.1.

Figure 5.1: Study flow diagram.



5.3.2 Characteristics of the included studies

No studies were identified in the literature comparing hepatectomy alone, with hepatectomy along with lymphadenectomy in patients with involved nodes. Therefore, a meta-analysis could not be performed comparing lymphadenectomy versus no lymphadenectomy in patients having liver resection for colorectal liver metastases with involved lymph nodes. Also, there were no studies comparing hepatectomy alone, with hepatectomy along with routine lymphadenectomy. Furthermore, there were no studies comparing hepatectomy with non-surgical treatments, such as chemotherapy or radiofrequency ablation, in patients with node positive disease who were otherwise suitable for hepatectomy.

Twenty-one non-randomised studies[28, 117-119, 197, 199, 201, 206-208, 217-227] reporting on patients who had undergone hepatectomy for CLM, and comparing the survival of node positive patients versus node negative patients, were included in the meta-analysis in order to determine the prognostic significance of hepatic lymph node status in patients undergoing hepatectomy for CLM. The studies were published between 1992 and 2013. In total, 4,618 patients undergoing hepatectomy for CLM were included in the meta-analysis: 391 patients were node positive and 4,227 patients were node negative. All included studies were at high risk of bias according to the criteria set in this meta-analysis. The risk of bias in the included studies is summarised in Figure 5.2 and Figure 5.3.

The characteristics of the included studies are shown in Table 5.1. The survival data of the individual studies is shown in Table 5.2. Routine lymphadenectomy was performed in 12 studies.[117-119, 199, 208, 217, 219-221, 223, 224, 227] Neoadjuvant chemotherapy was given in patients in 6 studies,[28, 207, 208, 221, 224, 226] and adjuvant chemotherapy in 15 studies.[28, 118, 119, 201, 206-208, 217-221, 223, 224, 226]

Figure 5.2: Risk of bias summary - review authors' judgments about each risk of bias item for each included study.

Footnotes: green plus sign = low risk of bias, yellow question mark = unclear risk of bias, red minus sign = high risk of bias.

Figure 5.3: Risk of bias graph - review authors' judgments about each risk of bias item presented as percentages across all included studies.

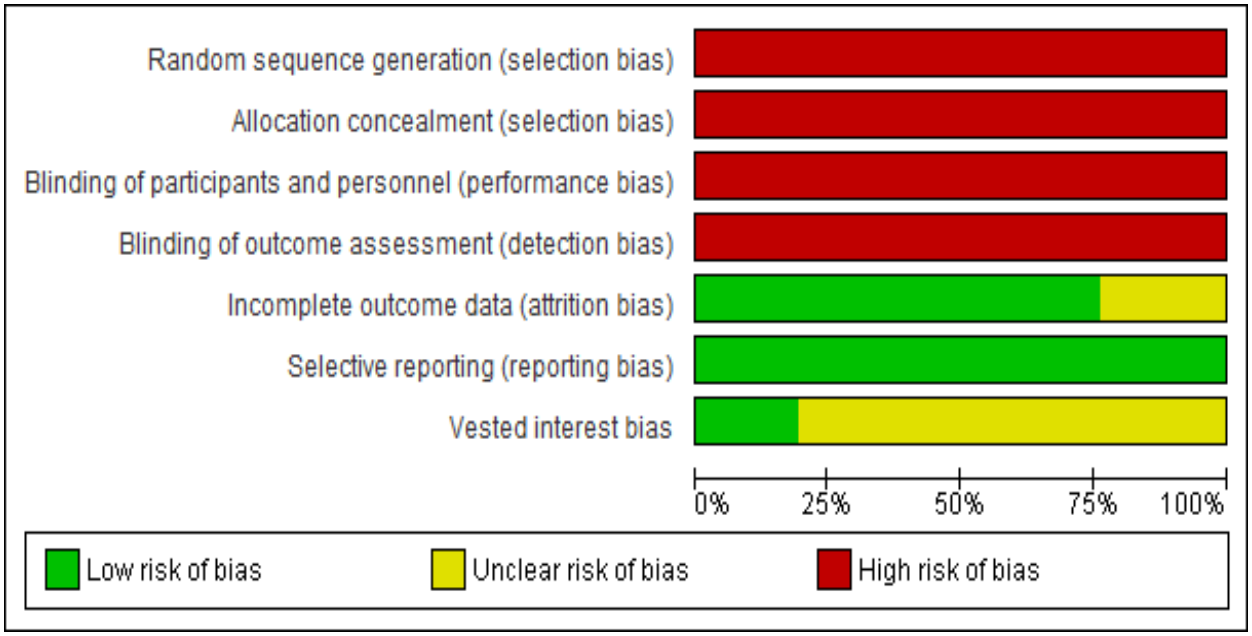


Table 5.1: Characteristics of the included studies reporting on patients who had undergone hepatectomy for CLM, and comparing the survival of node positive patients versus node negative patients.

Authors	Year	Total number of patients	Number of node positive cases (percentage)	Routine or selective lymphadenectomy	Microscopic or macroscopic node involvement or both	Group of nodes dissected	Chemotherapy	Indications for chemotherapy
Adam *et al.*	2008	763	47 (6.2)	Selective	Both	Pedicular, coeliac, para-aortic	Selective neoadjuvant and adjuvant	Poor prognostic factors
Ambiru *et al.*	1999	149	8 (5.4)	Routine	Both	Hepatoduodenal ligament	Adjuvant local or none	Not stated
Aoki *et al.*	2008	187	9 (4.8)	Selective	Both	Hepatoduodenal ligament	Adjuvant local or systemic or none	Not stated
Beckhurts *et al.*	1997	126	35 (27.8)	Routine	Both	Hepatoduodenal ligament	Not stated	Not stated
Bennett *et al.*	2008	45	8 (13.6)	Routine	Microscopic	Portocaval, pancreaticoduodenal, common hepatic artery	Selective neoadjuvant or adjuvant	Not stated
Carpizo *et al.*	2009	127	27 (21.3)	Not stated	Both	Portal lymph nodes (hepatoduodenal ligament, hepatic artery)	Adjuvant local or systemic or none	Not stated
Harms *et al.*	1999	155	39 (25.2)	Routine	Both	Hepatoduodenal ligament	Adjuvant local or systemic or none	Poor prognostic factors
Ishida *et al.*	2011	43	12 (27.9)	Routine	Both	Common hepatic, proper hepatic artery, superior border of pancreas	Adjuvant local or systemic	All
Jaeck *et al.*	2002	160	17 (10.6)	Routine	Both	Hepatic pedicle (hepatoduodenal ligament, retropancreatic, coeliac axis, hepatic artery)	Not stated	Not stated
Jonas *et al.*	2007	204	27 (13.2)	Routine	Both	Hepatoduodenal ligament	Adjuvant or neoadjuvant or none	Not stated
Kokudo *et al.*	1998	94	7 (7.4)	Not stated	Not stated	Hepatoduodenal ligament	Adjuvant local or systemic or none	Not stated
Laurent *et al.*	2004	156	23 (14.7)	Routine	Microscopic	Hepatic pedicle (hepatoduodenal, hepatic artery)	Adjuvant systemic	Not stated
Lupinacci *et al.*	2013	26	5 (19.2)	Routine	Microscopic	Hepatic hilum	Adjuvant	All
Minagawa *et al.*	2000	235	6 (2.6)	Selective	Both	Hepatic hilum	Not stated	Not stated

Table 5.1 continued

Nakamura *et al.*	1992	22	6 (27.3)	Routine	Microscopic	Hepatic pedicle (hepatoduodenal ligament, retropancreatic, coeliac axis)	Adjuvant systemic	All
Oussoultzoglou *et al.*	2008	132	12 (9.1)	Routine	Both	Hepatic pedicle	Adjuvant or neoadjuvant or none	Not stated
Pulitano *et al.*	2012	1519	61 (4.0)	Selective	Both	Hepatoduodenal ligament and retropancreatic area, common hepatic artery and celiac axis, para-aortic	Neoadjuvant and adjuvant	Not stated
Rosen *et al.*	1992	40	9 (22.5)	Selective	Both	Not stated	Not stated	Not stated
Sanchez-Cespedes *et al.*	1999	16	8 (50)	Not stated	Microscopic	Perihepatic	Not stated	Not stated
Settmacher *et al.*	2011	382	18 (4.7)	Not stated	Not stated	Not stated	Adjuvant or neoadjuvant or none	Not stated
Yasui *et al.*	1995	52	8 (15.4)	Routine	Both	Hepatic pedicle (hepatoduodenal ligament, retropancreatic, hepatic artery)	Not stated	Not stated

Table 5.2: Survival data of the included studies reporting on patients who had undergone hepatectomy for CLM, and comparing node positive patients versus node negative patients.

Author	Year	Total number of patients followed up for outcome	Node positive followed up				Node negative followed up			
			Total	1-year survival	3-year survival	5-year survival	Total	1-year survival	3-year survival	5-year survival
Adam *et al.*	2008	757	47	----	18 (38%)	8 (18%)	710	----	483 (68%)	376 (53%)
Ambiru *et al.*	1999	149	8	----	1 (12.5%)	1 (12.5%)	141	----	63 (44.7%)	38 (27.0%)
Aoki *et al.*	2008	187	9	----	5 (55.6%)	0 (0%)	178	----	87 (48.9%)	55 (30.9%)
Beckhurts *et al.*	1997	119	35	----	1 (2.9%)	0 (0%)	84	----	40 (47.6%)	19 (22.6%)
Bennett *et al.*	2008	45	8	----	2 (25%)	----	37	----	28 (75%)	----
Carpizo *et al.*	2009	127	27	----	8 (29.6%)	3 (11.1%)	100	----	67 (67%)	49 (49%)
Harms *et al.*	1999	155	39	----	1 (2.6%)	0 (0%)	116	----	52 (44.8%)	24 (20.7%)
Ishida *et al.*	2011	43	12	----	----	----	31	----	----	----
Jaeck *et al.*	2002	160	17	3 (17.6%)	3 (17.6%)	0 (0%)	143	135 (94.4%)	89 (62.2%)	67 (46.9%)
Jonas *et al.*	2007	204	27	----	7 (25.9%)	----	177	----	96 (54.2%)	----
Kokudo *et al.*	1998	94	7	6 (85.7%)	2 (28.6%)	0 (0%)	87	84 (96.6%)	57 (65.5%)	47 (54.0%)
Laurent *et al.*	2004	156	23	16 (69.6%)	6 (26.1%)	1 (4.3%)	133	117 (88%)	74 (55.6%)	57 (42.9%)
Lupinacci *et al.*	2013	26	5	----	----	----	21	----	----	----
Minagawa *et al.*	2000	235	6	0 (0%)	0 (0%)	0 (0%)	229	119 (52.0%)	89 (38.9%)	62 (27.1%)
Nakamura *et al.*	1992	21	5	----	2 (40%)	----	16	----	10 (62.5%)	----
Oussoultzoglou *et al.*	2008	132	12	----	4 (33.3%)	0 (0%)	120	----	88 (73.3%)	48 (40.0%)
Pulitano *et al.*	2012	1519	61	52 (85.2%)	21 (34.4%)	11 (18.0%)	1458	----	----	831 (57.2%)
Rosen *et al.*	1992	40	9	----	1 (11.1%)	0 (0%)	31	----	17 (54.8%)	11 (35.5%)
Sanchez-Cespedes *et al.*	1999	15	8	2 (25%)	0 (0%)	----	7	7 (100)	2 of 4 (50%)	----
Settmacher *et al.*	2011	382	18	----	----	----	364	----	----	----
Yasui *et al.*	1995	52	8	----	2 (25%)	0 (0%)	44	----	26 (59.1%)	18 (40.9%)

5.3.3 Overall results of meta-analysis

In total, 4,618 patients from 21 non-randomised studies[28, 117-119, 197, 199, 201, 206-208, 217-227] undergone hepatectomy for CLM were included in the meta-analysis: 391 patients had node positive disease and 4,227 patients had node negative disease.

The overall prevalence of positive hilar lymph nodes in the included studies was 8.5%, and the prevalence of patients with positive lymph nodes reported by all studies ranged between 2.6% and 50%. In patients who underwent hepatectomy for CLM along with routine lymphadenectomy the overall prevalence of positive lymph nodes was 15.7%, with a range between 5.4% and 27.9%. In studies where patients underwent hepatectomy for CLM along with selective lymphadenectomy the overall prevalence of positive lymph nodes was 4.8%, with a range of 2.6% to 22.5% (Table 1).

The overall 1-year, 3-year, and 5-year survival rates of patients who had undergone hepatectomy for CLM with positive lymph nodes were 64.8%, 23.6%, and 7.8%, respectively. The overall 1-year, 3-year, and 5-year survival rates of patients who had undergone hepatectomy for CLM with negative lymph nodes were 77.1%, 58.1% and 47.6%, respectively.

The odds of overall survival were significantly lower in the group of patients who had undergone hepatectomy for CLM with positive lymph nodes compared to the group of patients who had undergone hepatectomy for CLM with negative lymph nodes at 1 year (OR 0.09, 95% CI 0.05, 0.19; P<0.001), 3 years (OR 0.20, 95% CI 0.15, 0.27; P<0.001), and 5 years (OR 0.13, 95% CI 0.08, 0.19) (Figures 5.4, 5.5, and 5.6). There was significant heterogeneity between studies for overall survival at 1 year (P=0.008, I-square 71%), but only five studies were included in the analysis of that outcome. There was no significant heterogeneity between studies for overall survival at 3 years (P=0.31, I-square 12%) and 5 years (P=0.96, I-square 0%). Also, there was no evidence of publication bias based on visual assessment of the funnel plots (Figures 5.7, 5.8, and 5.9).

Figure 5.4: Overall meta-analysis - forest plot for the odds of overall survival at one year. Five studies reported on this outcome. The odds of overall survival at one year after hepatectomy for CLM were significantly lower in the group of patients with positive lymph nodes compared to the group of patients with negative lymph nodes.

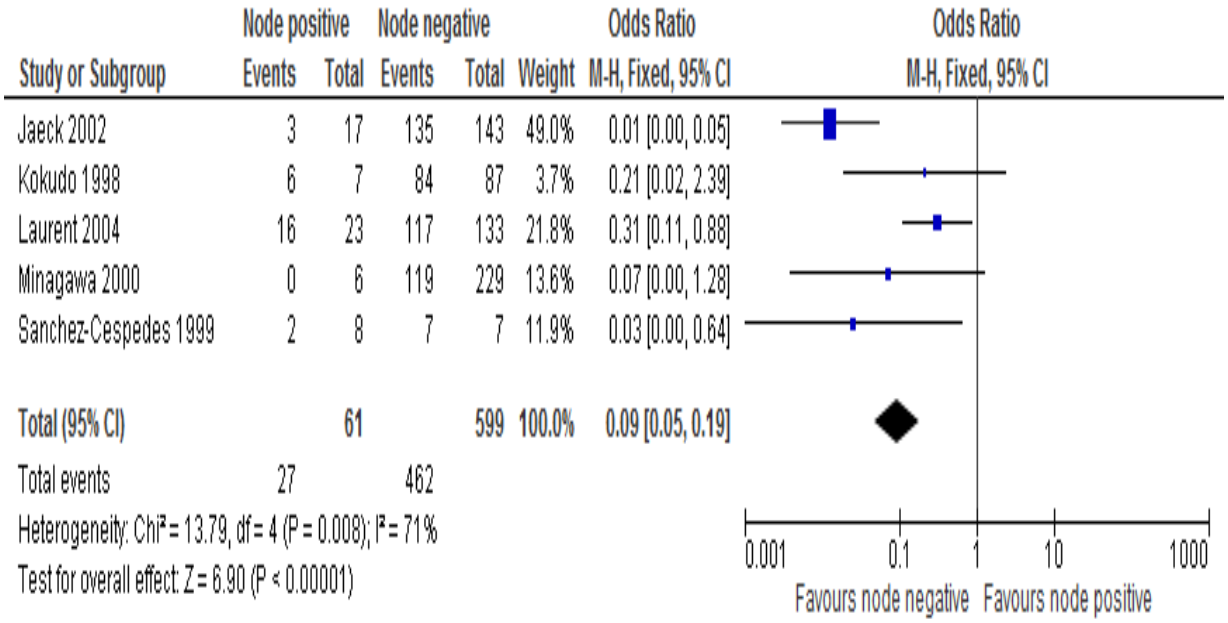


Figure 5.5: Overall meta-analysis - forest plot for the odds of overall survival at three years. The odds of overall survival at three years after hepatectomy for CLM were significantly lower in the group of patients with positive lymph nodes compared to the group of patients with negative lymph nodes.

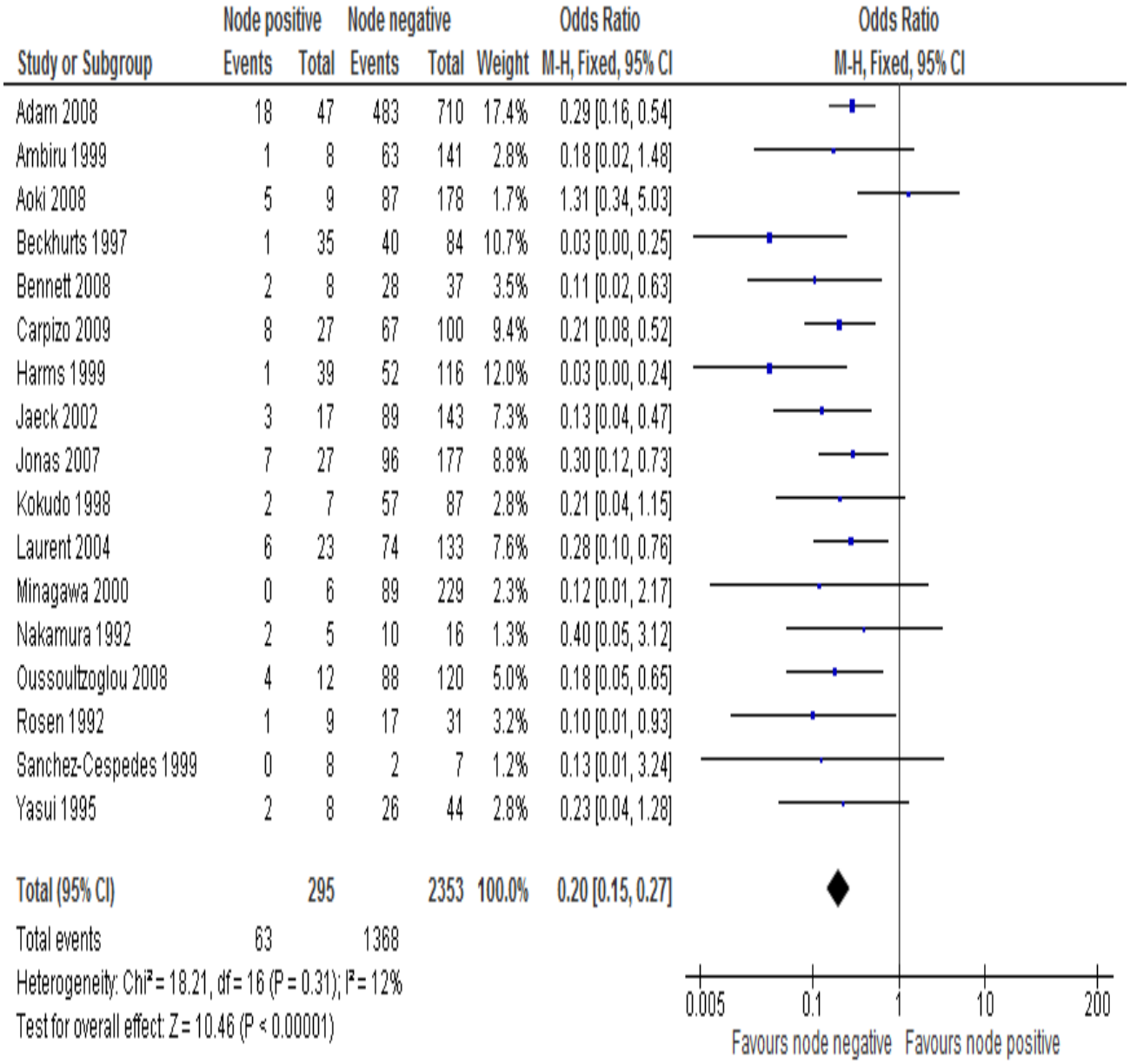


Figure 5.6: Overall meta-analysis - forest plot for the odds of overall survival at five years. The odds of overall survival at five years after hepatectomy for CLM were significantly lower in the group of patients with positive lymph nodes compared to the group of patients with negative lymph nodes.

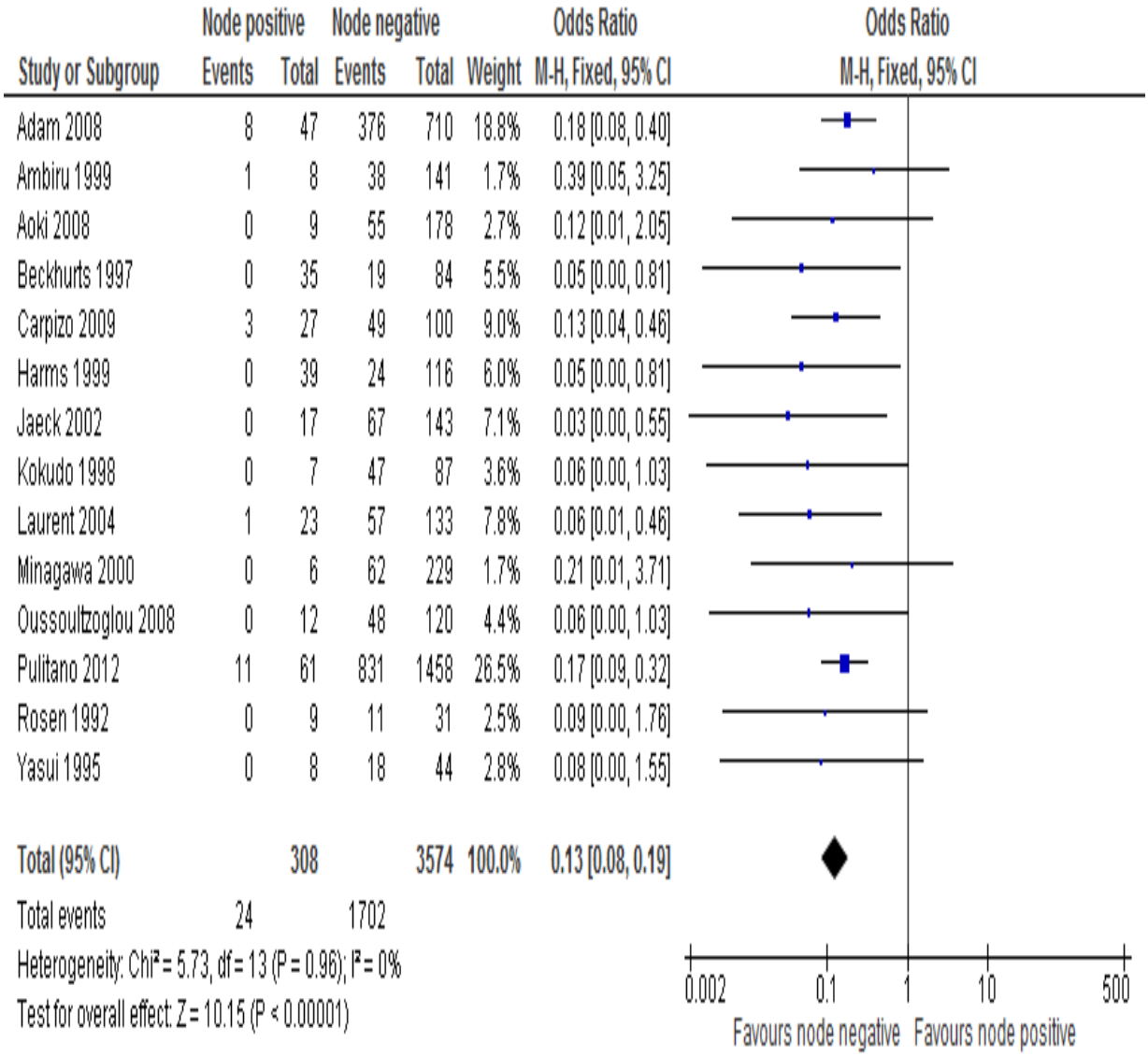


Figure 5.7: Overall meta-analysis - funnel plot for the odds of overall survival at one year after hepatectomy for CLM. There was no evidence of publication bias.

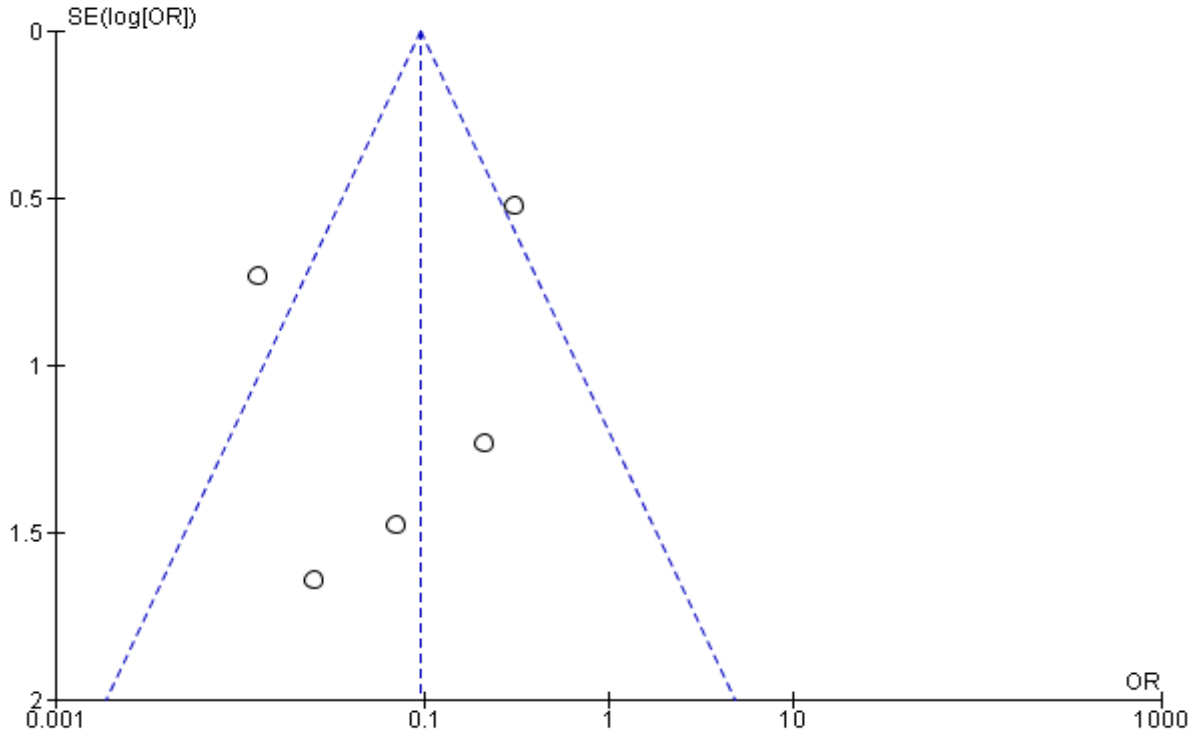


Figure 5.8: Overall meta-analysis - funnel plot for the odds of overall survival at three years after hepatectomy for CLM. There was no evidence of publication bias.

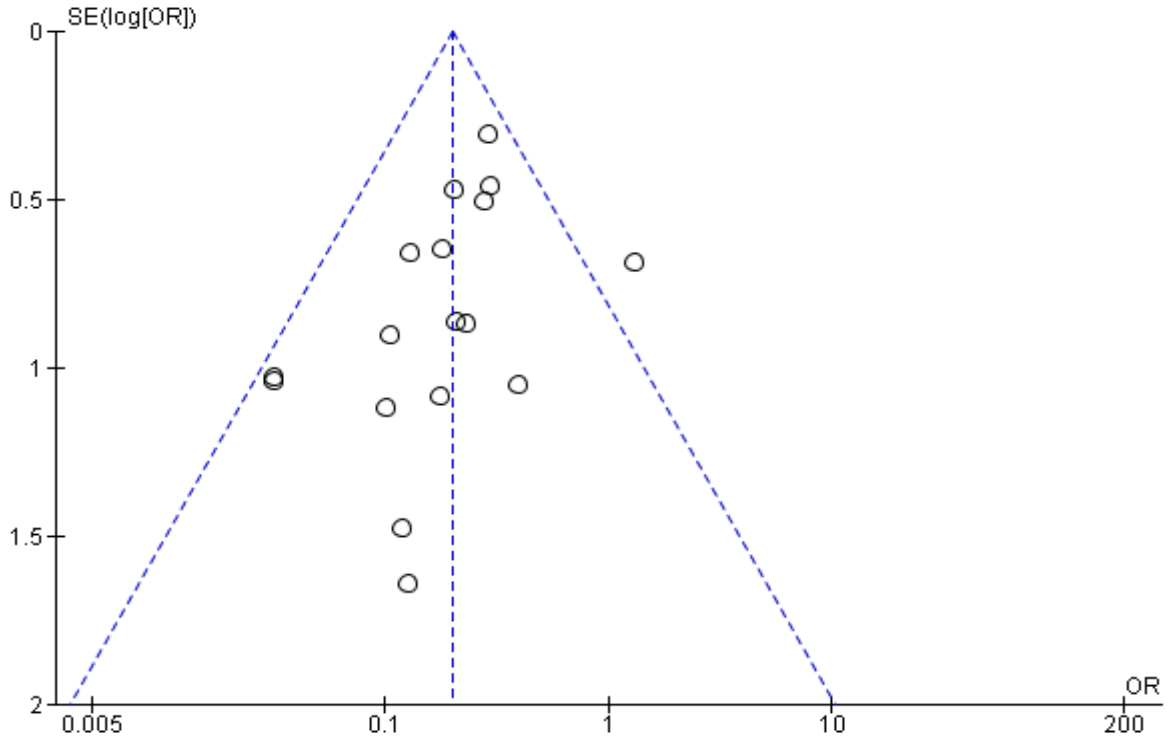
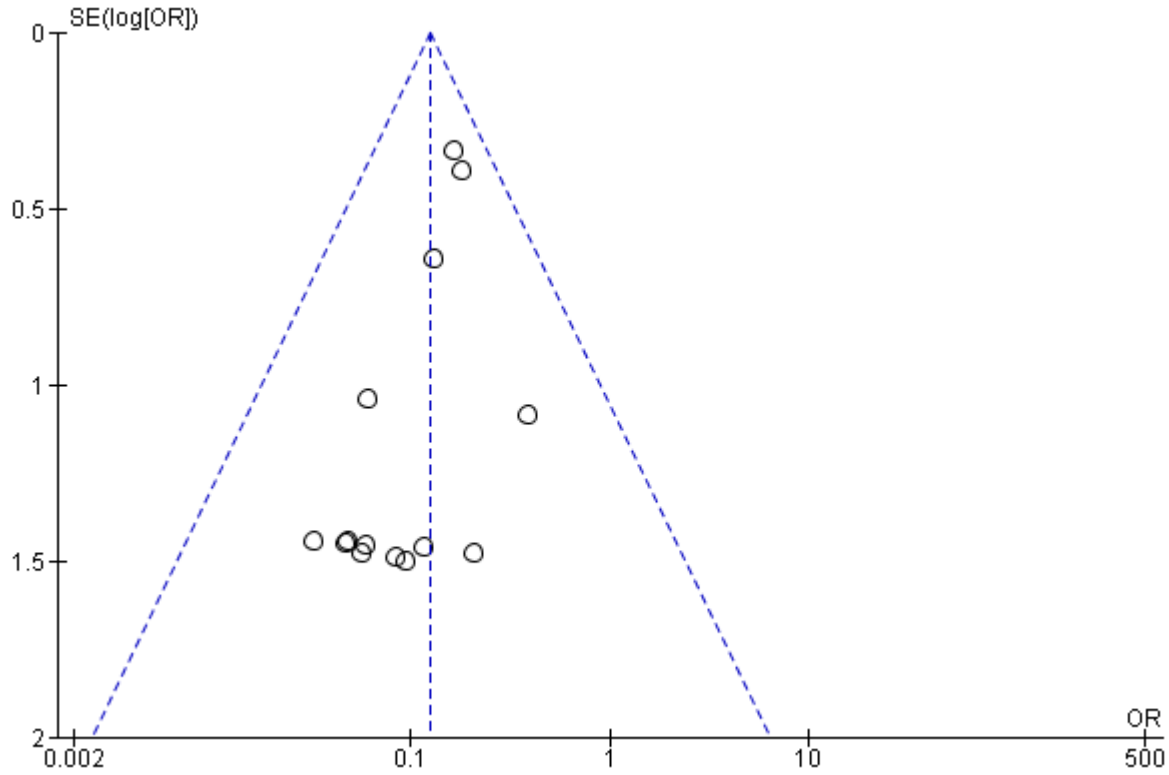


Figure 5.9: Overall meta-analysis - funnel plot for the odds of overall survival at five years after hepatectomy for CLM. There was no evidence of publication bias.



The overall survival rate of patients undergoing liver resection for CLM was found to be significantly lower in the group of patients with lymph nodes metastases compared to the group of patients with negative lymph nodes (fixed-effect model; HR 0.29, 95% CI 0.29, 0.29; P<0.001) with significant heterogeneity between studies (P<0.001, I-square 100%). The result was the same for the random-effects model (HR 0.35, 95% CI 0.25, 0.49; P<0.001) (Figure 5.10). As shown in Figure 5.10 the heterogeneity was in the magnitude of the effect rather than the direction. There was no evidence of publication bias as shown by the funnel plot in Figure 5.11.

Figure 5.10: Overall meta-analysis - forest plot for overall survival rate. The overall survival rate was significantly lower after hepatectomy for CLM in the group of patients with positive lymph nodes compared to the group of patients with negative lymph nodes with significant heterogeneity.

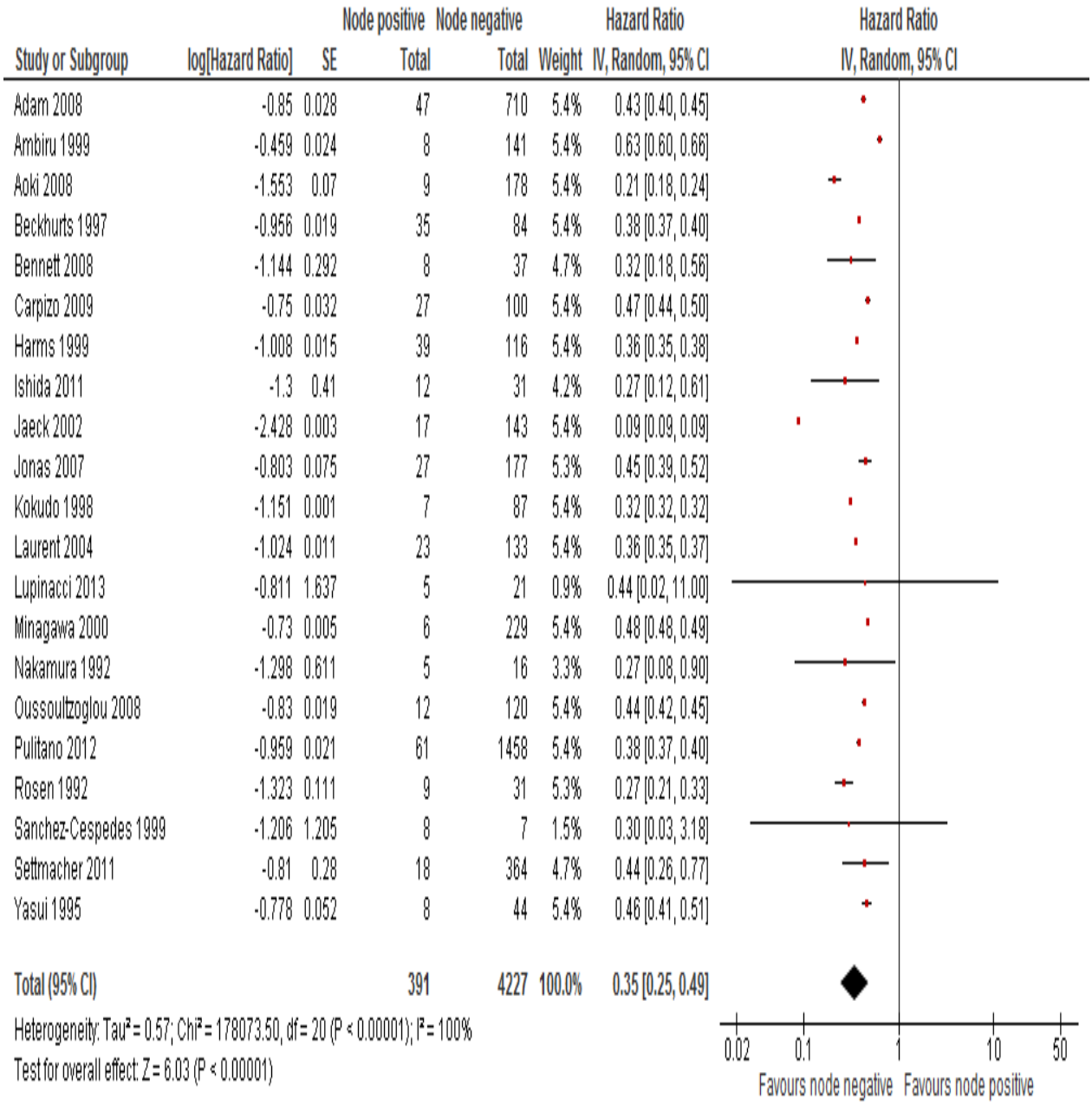
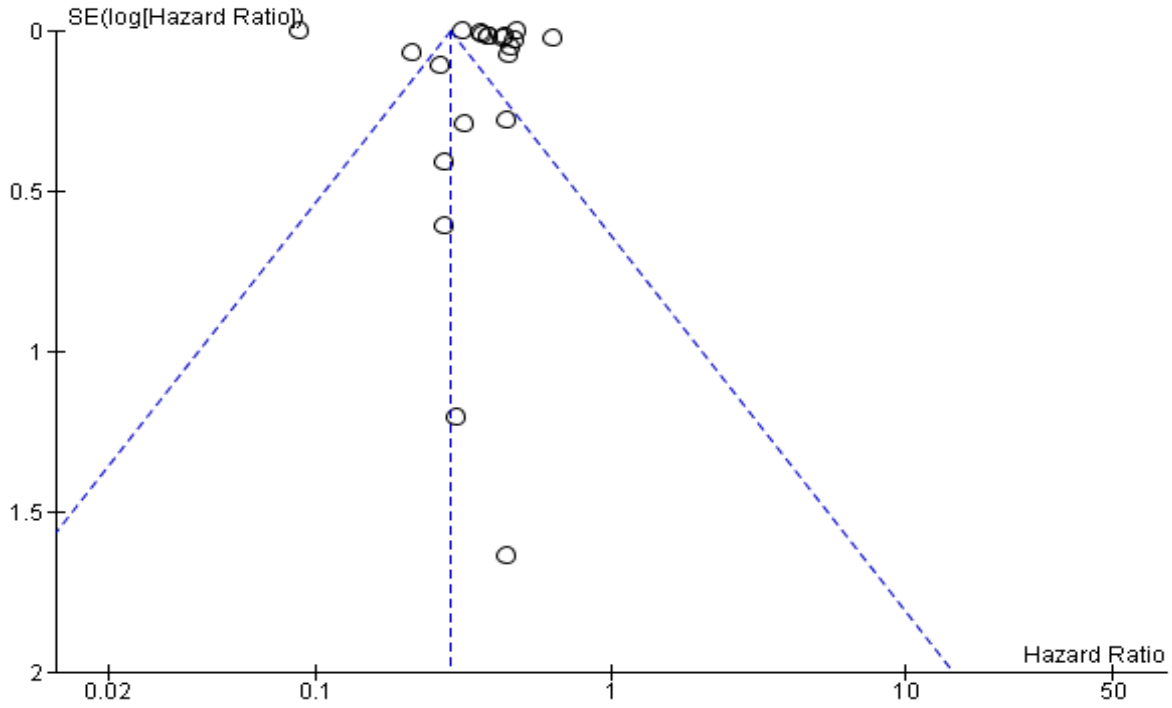


Figure 5.11: Overall meta-analysis - funnel plot for overall survival rate after hepatectomy for CLM. There was no evidence of publication bias.



5.3.4 Sensitivity analysis

The results of all the sensitivity analyses performed were similar to the overall meta-analysis results, demonstrating a significantly lower overall survival rate after hepatectomy for CLM for patients with node positive disease compared to patients with node negative disease.

Sensitivity analysis of studies including only patients with microscopic nodal involvement, showed a significantly lower overall survival rate after hepatectomy for CLM for node positive patients compared to node negative patients (HR 0.36, 95% CI 0.35, 0.37; P<0.001) with no significant heterogeneity between studies (P=0.98, I-square 0%) (Figure 5.12).

Sensitivity analysis of studies which included only patients in whom routine hepatic lymphadenectomy was performed, demonstrated a significantly lower overall survival rate after liver resection for CLM for patients with node positive disease compared to node negative disease (HR 0.11, 95% CI 0.11, 0.11; P<0.001), with significant heterogeneity in the magnitude of the effect (P<0.001, I-square 100%) (Figure 5.13).

In studies where adjuvant or neoadjuvant chemotherapy was used, the overall survival rate was significantly lower after liver resection for CLM for node positive patients compared to node negative patients (HR 0.32, 95% CI 0.32, 0.32; P<0.001), with significant heterogeneity in the magnitude of the effect (P<0.001, I-square 99%) (Figure 5.14).

Sensitivity analysis of more recent studies published after 2006, demonstrated a significantly lower overall survival rate after hepatectomy for CLM for patients with node positive disease compared to patients with node negative disease (HR 0.41, 95% CI 0.41, 0.42; P<0.001), with significant heterogeneity in the magnitude of the effect (P<0.001, I-square 93%) (Figure 5.15).

Figure 5.12: Sensitivity analysis of studies including only patients with microscopic nodal involvement - forest plot for overall survival rate. Node positive patients had significantly lower overall survival rate after hepatectomy for CLM compared to node negative patients.

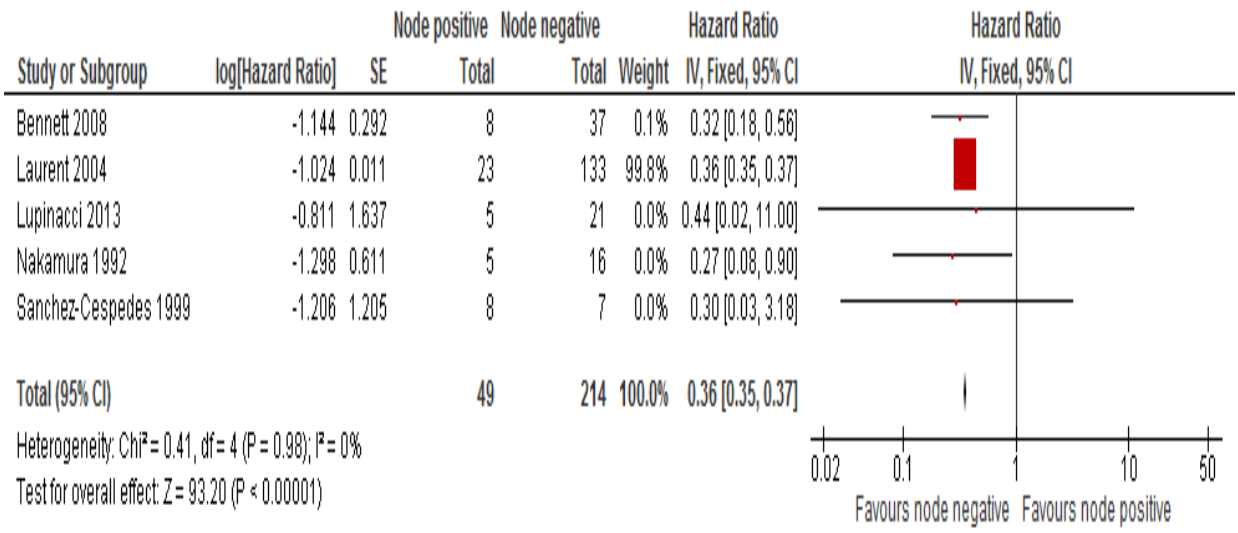


Figure 5.13: Sensitivity analysis of studies including only patients in whom routine hepatic lymphadenectomy was performed - forest plot for overall survival rate. Node positive patients had significantly lower overall survival rate after hepatectomy for CLM compared to node negative patients with significant heterogeneity between studies in the magnitude of the effect.

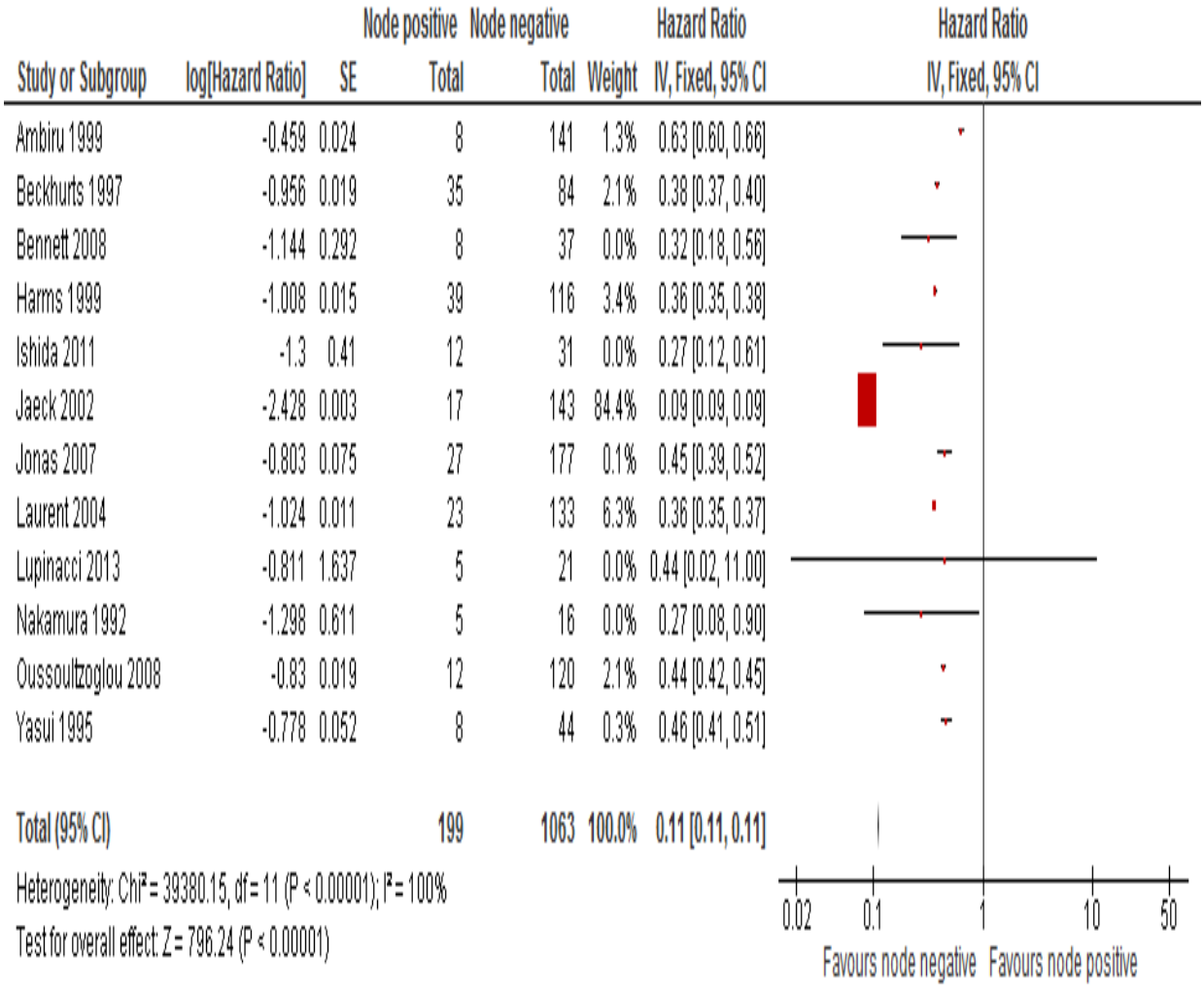


Figure 5.14: Sensitivity analysis of studies only where adjuvant or neoadjuvant chemotherapy was used - forest plot for overall survival rate. The overall survival rate was significantly lower after hepatectomy for CLM for node positive patients compared to node negative patients with significant heterogeneity in the magnitude of the effect.

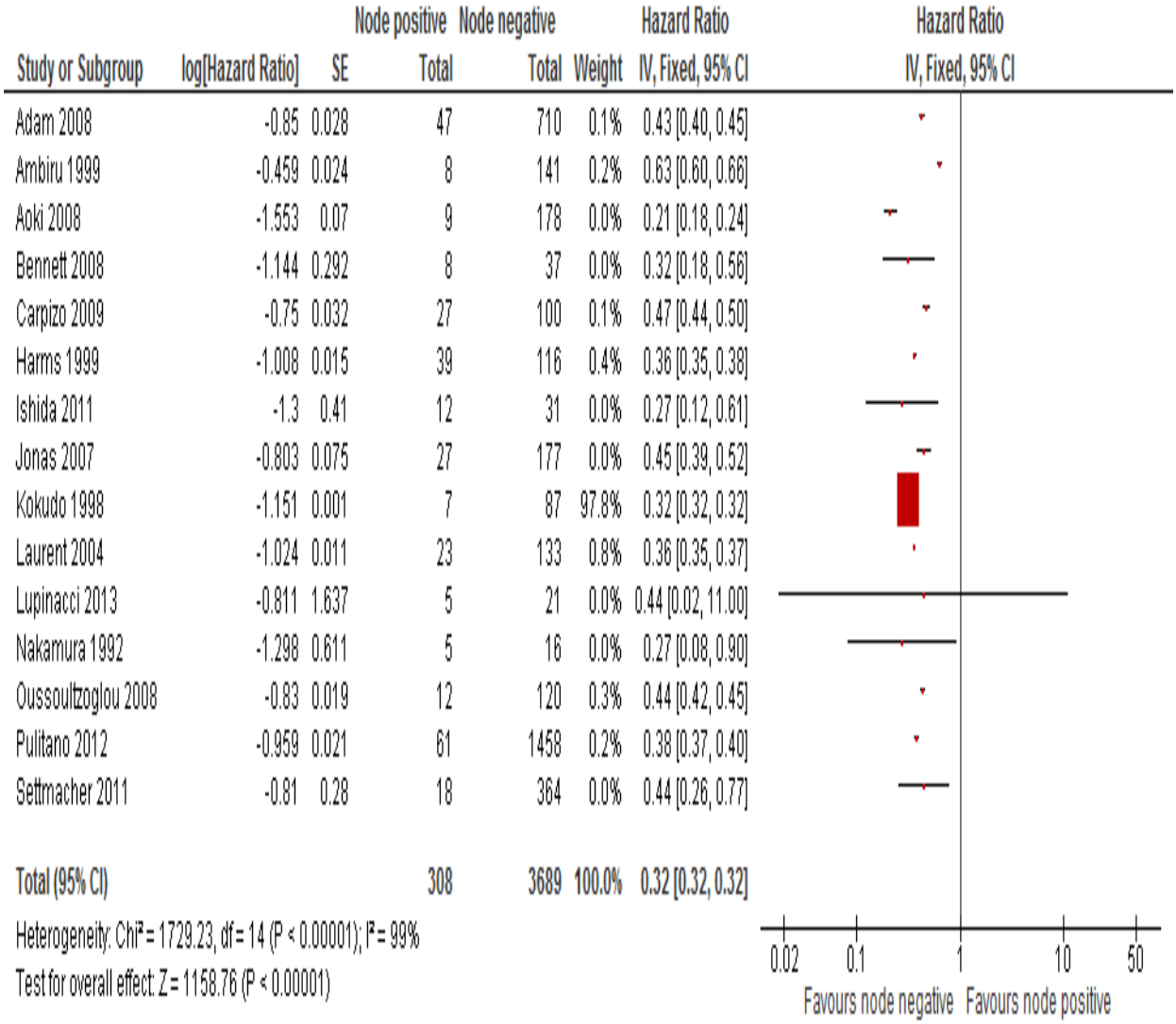
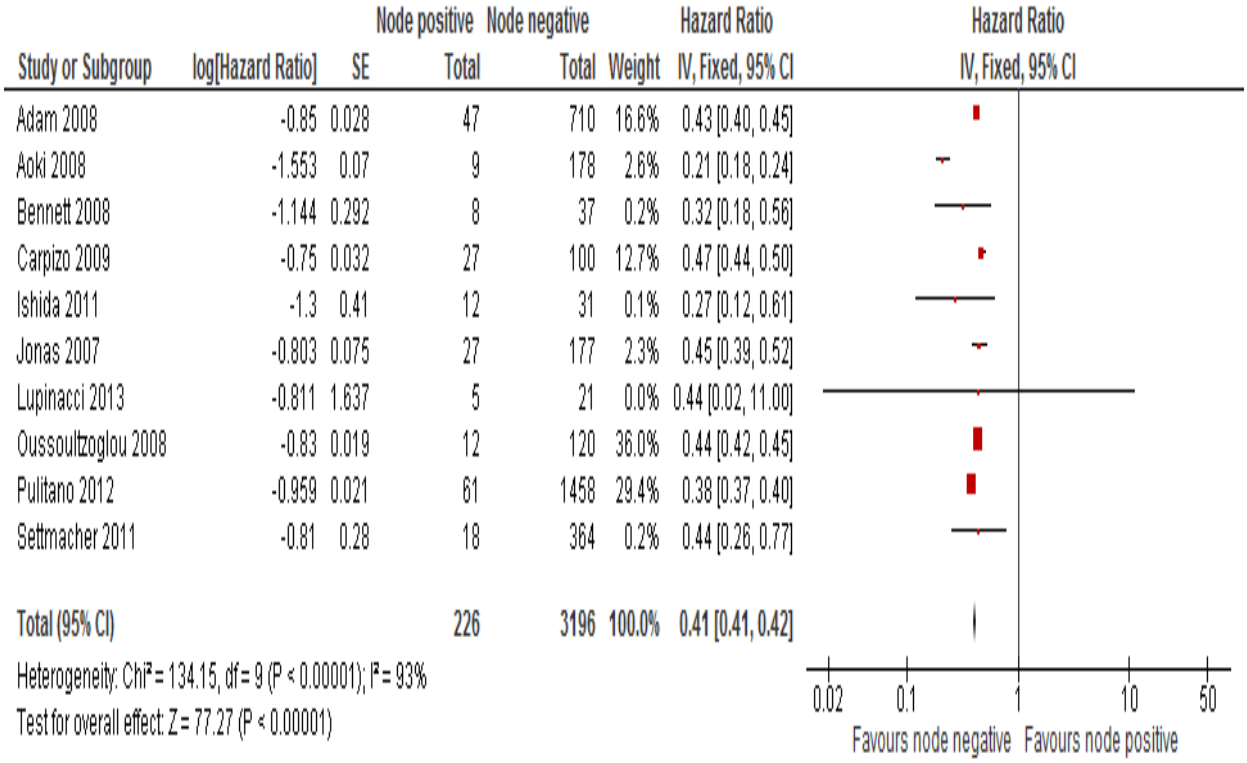


Figure 5.15: Sensitivity analysis of studies published after 2006 - forest plot for overall survival rate. Patients with node positive disease had significantly lower overall survival rate after hepatectomy for CLM compared to patients with node negative disease, with significant heterogeneity between studies in the magnitude of the effect.



In the subgroups classified by the extent/location of lymph node dissection, the overall survival rate of node positive patients was significantly lower compared to node negative patients, in patients who underwent:

- clearance of hilar or perihepatic lymph nodes only (HR 0.48, 95% CI 0.48, 0.49; P<0.001), with no significant heterogeneity between studies (P=0.92, I-square 0%) (Figure 5.16)
- clearance of hepatoduodenal lymph nodes only (HR 0.32, 95% CI 0.32, 0.32; P<0.001), with significant heterogeneity in the magnitude of the effect (P<0.001, I-square 100%) (Figure 5.17)
- clearance of hepatic pedicle lymph nodes only (HR 0.10, 95% CI 0.10, 0.10; P<0.001) with significant heterogeneity in the magnitude of the effect (P<0.001, I-square 100%) (Figure 5.18)

Figure 5.16: Sensitivity analysis of studies where patients underwent hepatectomy for CLM with clearance of hilar or perihepatic lymph nodes only - forest plot for overall survival rate. The overall survival rate of node positive patients was significantly lower compared to node negative patients.

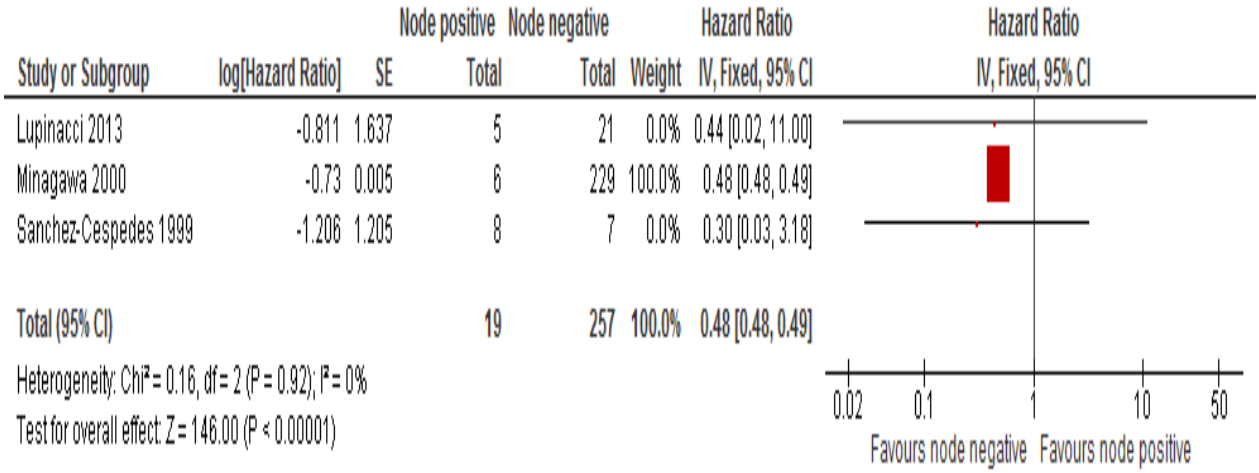


Figure 5.17: Sensitivity analysis of studies where patients underwent hepatectomy for CLM with clearance of hepatoduodenal lymph nodes only - forest plot for overall survival rate. The overall survival rate of node positive patients was significantly lower compared to node negative patients.

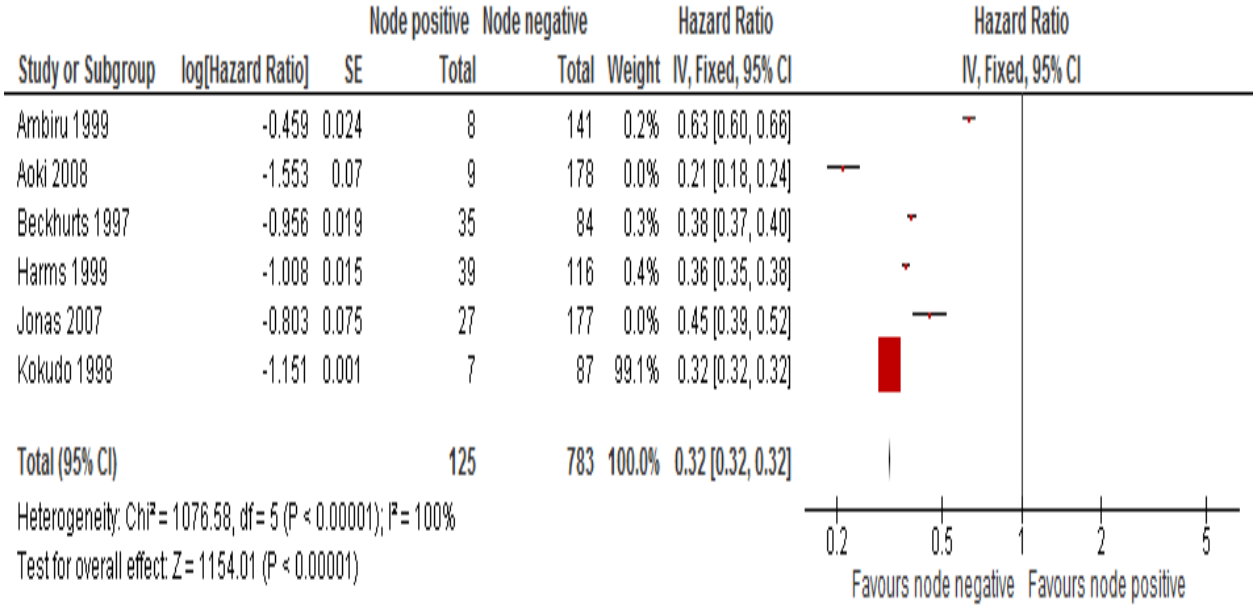
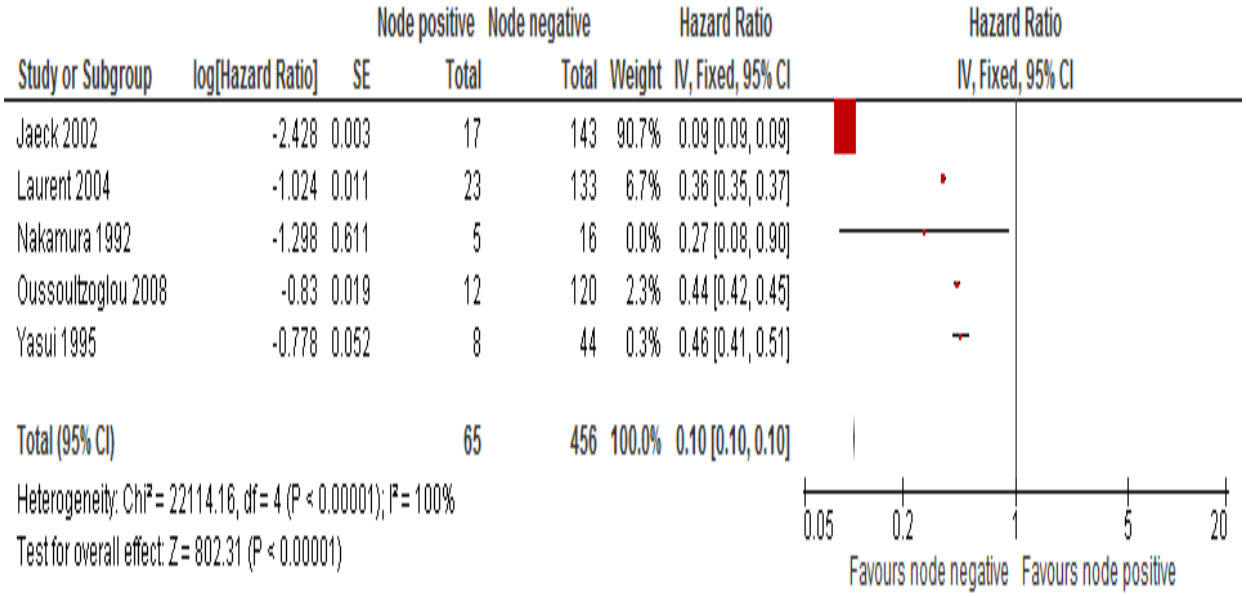


Figure 5.18: Sensitivity analysis of studies where patients underwent hepatectomy for CLM with clearance of hepatic pedicle lymph nodes only - forest plot for overall survival rate. The overall survival rate of node positive patients was significantly lower compared to node negative patients.



5.4 DISCUSSION

This meta-analysis included 21 non-randomised studies comparing patients who underwent hepatectomy for CLM with node positive disease versus patients with node negative disease. The meta-analysis has clearly demonstrated that the long-term survival was considerably higher in those undergoing hepatectomy with no involved hepatic lymph nodes than in those with hepatic lymph node metastases. The survival in the group of patients with positive lymph nodes was significantly reduced compared to patients with no nodal involvement, regardless of whether the nodal involvement was microscopic or macroscopic, and whether the nodal involvement was found at the time of routine or selective lymphadenectomy. Also, the survival of node positive patients compared to node negative patients was significantly reduced regardless of the use of adjuvant or neoadjuvant chemotherapy, and regardless of the extent/location of the lymph node dissection (i.e. hilar or perihepatic lymph nodes, hepatoduodenal lymph nodes, hepatic pedicle lymph nodes).

There have been no studies comparing liver resection along with lymphadenectomy versus nonsurgical treatments such as chemotherapy in patients with macroscopic evidence of node positive disease who were otherwise suitable for liver resection. Also, there have been no studies comparing liver resection alone versus liver resection along with lymphadenectomy in those with macroscopically involved nodes (selective lymphadenectomy). Similarly, there have been no studies comparing liver resection alone versus liver resection along with routine lymphadenectomy, and therefore, a survival analysis of liver resection for CLM with, versus without routine lymphadenectomy, could not be performed. Routine lymphadenectomy is generally performed in order to remove the microscopically involved lymph nodes draining the liver and provide cancer clearance, and also in order to guide adjuvant chemotherapy regimens. The studies which involved routine lymphadenectomy[117-119, 199, 208, 217, 219-221, 223, 224, 227] reported very poor or no 5-year survival in patients with nodal disease compared with node negative patients.

Unfortunately, there was no morbidity data directly related to lymphadenectomy by the included studies available for meta-analysis. It would be important to know the additional risks to the patient by routine or selective lymphadenectomy. Although lymphadenectomy is generally considered to be a safe procedure in experienced hands,

it is associated with potential risks and complications such as portal vein injury, duodenal injury, lymphatic leakage and bleeding.[228] Two studies[28, 117] compared morbidity in those who underwent lymphadenectomy with those who did not, and they reported no difference in morbidity between the two groups. None of the included studies reported complications directly related to hepatic lymphadenectomy, and none of the included studies reported higher mortality with lymphadenectomy. Furthermore, there was no data available by the included studies on the extent of recurrent disease, as it would have been important to know how recurrent disease presents (i.e. more extensive disease, more liver metastases or more extensive lymphatic dissemination) and whether there would be a difference in recurrent disease between patients who had resection of nodal metastases.

The overall prevalence of positive lymph nodes identified in the current review was 8.5%. However, the prevalence reported by the included studies varied between 2.6% and 50%. Some surgeons remove only the lymph nodes along the hepatoduodenal ligament,[199, 217, 219] whilst others remove nodes along the common hepatic artery, coeliac artery, and the retropancreatic area.[117] The prevalence of positive lymph nodes in the eight studies[119, 199, 201, 217-219, 221, 222] which reported hepatoduodenal/hepatic hilum lymph node dissection ranged between 2.6% and 27.8%, and the prevalence of positive lymph nodes in the ten studies[28, 117, 118, 206-208, 220, 223, 224, 227] which reported more extensive lymph node dissection of the hepatic pedicle and retropancreatic area, ranged between 4% and 27.9%. Therefore, the extent of the lymphadenectomy was not the main factor that causes the difference in the prevalence rate of node positive disease between studies.

The prevalence of patients with positive lymph nodes in the twelve studies[117-119, 199, 208, 217, 219-221, 223, 224, 227] reporting routine lymphadenectomy ranged between 5.4% and 27.9%, and the prevalence of positive nodal disease in the five studies[28, 207, 218, 222, 225] which reported selective lymphadenectomy ranged between 2.6% and 22.5%. Thus, the routine or selective approach for lymphadenectomy appears also not to be the main factor causing the variation in prevalence of disease positive lymph nodes between the included studies.

The wide variation in prevalence of disease positive lymph nodes may be influenced by other factors, for example, patient selection for surgery, the adequacy of pre-operative

staging, preoperative and intraoperative assessment, the number of nodes examined, the number of sections per node, and neoadjuvant chemotherapy. Another factor which may influence the prevalence of node positive disease is the use of special techniques to identify microscopic involvement to detect positive lymph node disease. Two studies found increased sensitivity for detection of micrometastases in perihepatic lymph nodes by adding immunohistochemistry analysis[208] and molecular-based techniques.[197] Larger studies are required to assess the value and relevance of these techniques of detecting nodal disease in routine clinical practice.

Three studies[28, 117, 207] compared survival of patients with positive nodes in different locations and all three found better outcome in patients with hepatoduodenal lymph node involvement against those with coeliac and para-aortic lymph node involvement. Importantly, Adam *et al.*[28] and Pulitano *et al.*[207] found exceptionally poor survival in patients with coeliac and para-aortic node involvement despite preoperative chemotherapy. Adam *et al.*[28] found a better 5-year survival rate (25%) for patients who underwent hepatectomy and lymphadenectomy of involved hepatic pedicle lymph nodes than for those undergoing hepatectomy along with resection of involved coeliac and para-aortic lymph nodes (0%). Jaeck *et al.*[117] reported that in their cohort of 17 patients in whom lymph node involvement was diagnosed after routine lymphadenectomy during liver resection, the 3-year survival rate was 38% in patients who had nodal involvement in the hepatoduodenal ligament compared with 0% in patients who had nodal involvement around the hepatic artery and coeliac trunk. Involvement of common hepatic artery and coeliac artery nodes carries a worse prognosis compared to hepatoduodenal ligament nodal involvement, and coeliac and para-aortic lymph node disease should be considered an absolute contraindication to surgery. Whereas, selected patients with hepatoduodenal ligament nodal involvement only, who responded to neoadjuvant treatment, may be candidates for surgery, and future trials should further investigate this hypothesis.

There is variation between studies in the reported benefit of adjuvant chemotherapy in patients already undergone hepatectomy for CLM and were found to have nodal metastases on a routine or selective lymphadenectomy. In the study by Nakamura *et al.*[223], all the patients in the study received chemotherapy. The 3-year survival in the 6 patients with positive hepatic lymph node was 33.3% (the study did not report the 5-year survival).[223] In the study by Harms *et al.*[219] in which chemotherapy was given in

patients with poor prognostic factors, the 3-year and 5-year survival of hepatic node-positive patients was 2.6% and 0%. Pulitano *et al.*[207] found 3-year and 5-year overall survival rates of 34% and 18%, respectively, in 61 patients with node positive disease, most of whom had received neoadjuvant as well as adjuvant chemotherapy. Adam *et al.*[28] suggested that the 5-year survival rate of 18% in node positive patients reported in their study may be related to neoadjuvant chemotherapy and patient selection based on absence of progression of nodal disease preoperatively. The survival benefit was seen in patients with pedicular lymph node involvement and not in patients with coeliac and para-aortic node involvement. There is a possibility that hepatectomy along with resection of metastatic lymph nodes in highly selected patients based on their response to neoadjuvant chemotherapy and based on the extent/location of the lymph node dissection (pedicular lymph nodes instead of coeliac/para-aortic lymph nodes) may benefit from surgical resection and chemotherapy. Nevertheless, to justify this statement a study should be performed comparing the outcome of node positive patients selected for hepatectomy based on their response to neoadjuvant chemotherapy versus node positive patients who had undergone hepatectomy for CLM without neoadjuvant chemotherapy.

Sensitivity analysis of more recent studies published after 2007 still showed a significant decrease in survival rate after hepatectomy for CLM for patients with node positive disease compared to patients with node negative disease. Nevertheless, it is interesting that three studies with significantly improved 5-year survival rates were published more recently. Adam *et al.* with 5-year survival rate of 18% was published in 2008, Carpizo *et al.* with 5-year survival rate of 11.1% was published in 2009, and Pulitano *et al.* with 5-year survival rate of 18% was published in 2012. It is possible that modern chemotherapy has an impact on survival in hepatic pedicular lymph node positive patients, but this needs to be demonstrated in large and properly designed clinical trials. In the past, with 5-fluorouracil and leucovorin based chemotherapy for CLM, the response rate was 20% to 30%, with a median survival time of 11 to 12 months.[229] With the advent of more effective systemic agents such as oxaliplatin, irinotecan, cetuximab and bevacizumab, improved response rates of 33% to 62%, median overall survival time of more than 20 months, and improved progression-free survival are now seen in patients with CLM.[229, 230]

These developments in modern chemotherapy may have an impact on results of surgical resection in patients with extrahepatic disease, and with more effective therapies there may be an indication for both liver resection and lymphadenectomy in those with chemotherapy-sensitive disease.[230] Neoadjuvant chemotherapy has been used to downstage previously non-resectable metastatic colorectal cancer (the reasons for non-resectability included extra-hepatic disease in the lungs and lymph nodes) with reasonable three-year results.[16, 28, 29] Neoadjuvant chemotherapy is being used in other node-positive tumours including oesophageal cancers[231, 232] and rectal cancers[233, 234] for downstaging the disease preoperatively and may improve the median survival.[231] It is not clear whether neoadjuvant chemotherapy will be useful in improving the survival in people with CLM and node positive disease. The role of neo-adjuvant chemotherapy in patients with CLM with hepatic node involvement needs to be evaluated in a prospective trial.

Surgeons offering hepatectomy along with hepatic lymphadenectomy for resectable CLM associated with hepatic lymph node metastases must inform their patients that the surgery is without evidence of a survival advantage. The alternative to surgery for patients with resectable CLM in the face of known hepatic nodal metastases is to undergo systemic chemotherapy, and currently, there is no evidence that liver resection is superior to chemotherapy. Patients in whom liver resection along with lymphadenectomy is being considered should be counselled and should be made aware that the procedure is not part of routine clinical practice and is unlikely to be curative. The procedure would ideally be performed as part of a clinical study or trial. Patients with prior response to systemic chemotherapy, with resectable CLM combined with hilar nodal involvement could be considered for an RCT offering surgical resection (liver resection and lymphadenectomy) and chemotherapy versus chemotherapy alone. Also, patients with CLM and hepatic nodal involvement could be considered for a RCT comparing liver resection along with lymphadenectomy and chemotherapy versus radiofrequency ablation of CLM along with chemotherapy.

5.5 CONCLUSIONS

This meta-analysis has clearly demonstrated that the survival rates of patients who had undergone hepatectomy for CLM are lower in patients with positive hepatic lymph nodes compared to patients with negative lymph nodes. This is irrespective of whether they are detected by routine or selective lymphadenectomy, or whether the nodal involvement was microscopic or macroscopic. Also, the decreased survival of node positive patients compared to node negative patients is regardless of the use of adjuvant or neoadjuvant chemotherapy, and of the extent/location of the lymph node dissection. Currently, there is no evidence of survival benefit from routine lymphadenectomy in patients with resectable CLM. Furthermore, in patients with CLM associated with hepatic nodal metastases, liver resection and lymphadenectomy is of no proven benefit and has not been compared with systemic chemotherapy or with radiofrequency ablation. Further trials in this patient group are required.

CHAPTER 6

A NETWORK META-ANALYSIS COMPARING TREATMENT STRATEGIES USED DURING LIVER RESECTION AIMING TO DECREASE BLOOD LOSS AND BLOOD TRANSFUSION

6.1 INTRODUCTION

Liver resection is the only curative option for people with CLM, but is a major surgical procedure with significant mortality of around 4% and morbidity of around 40%.[45, 46, 63] As the liver is a very well-vascularized organ, there is an inherent risk of bleeding during liver resection. Intraoperative haemorrhage remains one of the major risks during liver resections, and operative blood loss and perioperative blood transfusion are two of the most important factors affecting perioperative morbidity and mortality.[45, 46, 64, 65] Variable estimates of blood loss, ranging from 200 mL to 2 litres, have been reported.[66] Major blood loss during surgery or in the immediate postoperative period may result in death of the patient.

Even small differences in operative blood loss and perioperative blood transfusion may result in increased morbidity and mortality. In a study by Ibrahim *et al.* hepatic donors with complications had a mean operative blood loss of 170±79 ml (mean ± standard deviation) compared to hepatic donors without complications who had a mean operative blood loss of 95±77 ml.[64] Also, Poon *et al.* demonstrated a significant decrease in morbidity from 37.3% to 30.0% and a significant decrease in mortality from 7.5% to 3.7%, in a group of patients who had undergone hepatectomy with a median operative blood loss of 750 ml and 17.3% perioperative transfusion, compared to another group with a median operative blood loss of 1450 ml and 67.7% perioperative transfusion.[46] Furthermore, Yang *et al.* demonstrated that increased intraoperative blood loss (≥ 800 ml) during major hepatic resection is an independent risk factor of postoperative morbidity.[65] Therefore, minimizing operative blood loss and perioperative blood transfusion is of major importance, and various interventions have been attempted to decrease blood loss during liver resection.

Interventions aiming to decrease blood loss during elective liver resection include methods of temporary occlusion of the blood vessels that supply the liver. Clamping of the portal pedicle (Pringle manoeuver, i.e. clamping of the hepatic artery and portal vein) is the oldest and commonest method of hepatic vascular occlusion during liver resection, and can be performed either continuously or intermittently during the parenchymal resection.[67-69] Also, different methods of liver transection (the way that the liver parenchyma is divided) have been used to reduce blood loss, such as the clamp-crush method, the Cavitron Ultrasonic Surgical Aspirator (CUSA), or the

radiofrequency dissecting sealer. In addition, different methods of management of the cut surface of the liver (the way that the resection plane of the remnant liver is managed) have been used, such as the use of fibrin sealant, argon beamer, or electrocautery and suture material.[66, 70] Commonly used surgical techniques under each of the above categories are listed in Table 6.1, Table 6.2, and Table 6.3.

Interventions selected to decrease blood loss and blood transfusion can be used alone or in various combinations. Usually surgeons at different centres follow their own protocol for decreasing blood loss during elective liver resection, and may use a particular combination of the different methods of vascular occlusion, of the different methods of parenchymal transection, and of the different methods of dealing with the raw surface of the liver after transection. Therefore, in liver resection, a surgeon typically uses one item from Table 6.1, one item from Table 6.2, and one item from Table 6.3. In practice, any intervention in Table 6.1 can be used in combination with an intervention from Table 6.2 or Table 6.3. Any intervention in Table 6.2 can be used in combination with an intervention from Table 6.1 or Table 6.3, etc. Together, one can consider this combination of one method from each table as a treatment strategy. Altogether, the goal of these interventions is to decrease blood loss and blood transfusion, and the associated morbidity and mortality.

Table 6.1: Different methods of vascular occlusion aiming to decrease blood loss during liver resection.

No vascular occlusion
Portal triad clamping (continuous) (occlusion of inflow alone)
Portal triad clamping (intermittent) (occlusion of inflow alone)
Hepatic vascular exclusion (occlusion of inflow and outflow)
Selective vascular occlusion (occlusion of inflow to the hemi-liver that is being resected)
Selective hepatic artery occlusion (occlusion of hepatic artery supplying the hemi-liver that is being resected)
Selective portal vein occlusion (occlusion of portal vein supplying the hemi-liver that is being resected)
Selective hepatic vascular exclusion (occlusion of inflow to the hemi-liver and outflow from the hemi-liver that is being resected)

Table 6.2: Different methods of parenchymal transection aiming to decrease blood loss during liver resection.

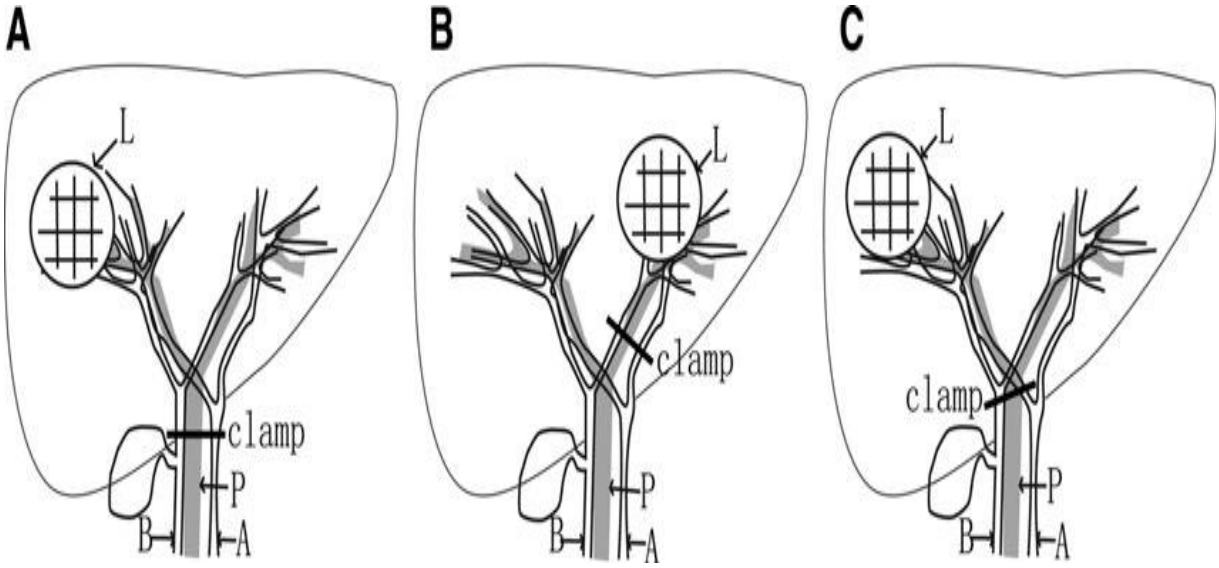
Finger-fracture method
Clamp-crush method
Cavitron Ultrasonic Surgical Aspirator (CUSA)
Sharp dissection
Radiofrequency dissecting sealer
Hydrojet
Ultrasonic shears

Table 6.3: Different methods of dealing with raw surface aiming to decrease blood loss during liver resection.

Suturing for large and medium vessels and ducts and performing electrocauterisation of small vessels and ducts
Suturing for large vessels and performing ultrasonic shears for medium-sized and small vessels and ducts
Suturing and argon beam coagulator
Suturing and fibrin sealant

Previous studies published in the literature compared individual components aiming to decrease operative blood loss and perioperative blood transfusion. Nuzzo *et al.* compared liver resections with or without hepatic pedicle clamping and found significantly fewer people requiring blood transfusion and significantly lower number of blood units transfused per patient when hepatectomy was performed with hepatic pedicle clamping.[235] Tan *et al.* compared different methods of hepatic inflow occlusion aiming to decrease blood loss and blood transfusion.[236] The three different methods were: intermittent total hepatic pedicle occlusion (or Pringle manoeuvre or portal triad clamping, i.e. clamping of portal vein and hepatic artery), hemihepatic vascular occlusion (or selective vascular occlusion, i.e. occlusion of the lesion-lateral portal vein and hepatic artery), and selective hepatic artery occlusion (i.e. occlusion of the portal vein and the lesion-lateral hepatic artery). A schematic drawing of these three different methods of hepatic inflow occlusion is shown in Figure 6.1. The study showed no significant difference in blood loss, clamping time, or operative time, between the three different methods of hepatic inflow occlusion. Hemihepatic vascular occlusion and selective hepatic artery occlusion caused significantly less liver remnant ischemia injury compared to intermittent total pedicle occlusion.[236] The authors concluded that hemihepatic vascular occlusion is easy to do for left lateral lobe or resection of the left half of the liver, and selective hepatic artery occlusion is suitable for right lobe resection.[236]

Figure 1: Schematic drawing of hepatic inflow occlusion: (A) Intermittent total pedicle occlusion, (B) hemihepatic vascular occlusion, and (C) selective hepatic artery occlusion (taken from Tan *et al.*).[236] Footnotes: A=hepatic artery; B=biliary duct; L=liver lesions; P=portal vein.



A RCT by Fu *et al.* compared Pringle manoeuver, hemihepatic vascular inflow occlusion, and main portal vein inflow occlusion during partial hepatectomy, and demonstrated no significant differences between the three groups in intraoperative blood loss, perioperative mortality.[237] The degree of postoperative liver injury and complication rates were significantly higher in the Pringle manoeuver group, resulting in a significantly longer hospital stay.[237] A study by Narita *et al.* included patients with chemotherapy-associated liver injury undergoing major hepatectomy for CLM, and compared patients who underwent intermittent portal triad clamping versus patients who did not undergo portal triad clamping.[238] The study showed that intraoperative blood transfusion and postoperative liver function were comparable between the two groups, and that prolonged portal triad clamping (>30 minutes) is related to increased postoperative biliary and septic complications.[238] A RCT by van den Broek *et al.* compared the effect of 15 versus 30 minute intermittent Pringle manoeuver during liver surgery using liver fatty acid-binding protein (L-FABP) as a sensitive marker of

hepatocellular damage.[239] The trial found no significant differences between 15 and 30 minute Pringle manoeuver in cumulative L-FABP level or L-FABP level at any time point (p=0.149).[239] Also, there was no significant difference between the two groups in operative blood loss, remnant liver function, or morbidity.[239] Furthermore, Wang *et al.* compared intermittent Pringle manoeuver versus continuous Pringle manoeuver coupled with in situ hypothermic perfusion, and demonstrated no difference between the two groups in operative time, blood loss, postoperative hospital stay, morbidity rate, and postoperative liver function.[240]

Mbah *et al.* compared bipolar compression and ultrasonic devices used for parenchymal transection during laparoscopic liver resection and noted no significant differences between the two device groups for blood loss, complications of any type, or liver-specific complications.[241] The bipolar compression device was found to result in significantly shorter time of parenchymal transection compared to the ultrasonic device.[241] A RCT by Doklestic *et al.* compared three different parenchyma transection techniques of liver resection: clamp crushing technique, ultrasonic dissection (CUSA), or bipolar device (LigaSure). The overall surgery duration was 295 *vs.* 270 *vs.* 240 minutes for LigaSure, CUSA and clamp crush, respectively; the transection duration was 85 *vs.* 52.5 *vs.* 40 minutes, respectively.[242] There were no significant differences between the three different resection techniques in terms of intraoperative blood loss, blood transfusion, postoperative complications, and mortality.[242] Moreover, Richter *et al.* compared liver resection using either ultrasonic dissection, hydrojet dissection, or radiofrequency dissecting sealer, and found the dissection was slower with the radiofrequency dissecting sealer; otherwise, the three devices were equally safe in terms of blood loss, transfusions, and postoperative complications.[243]

Kobayashi *et al.* compared the application of a fibrin sealant with polyglycolic acid on the transection plane of the liver after hepatectomy versus no fibrin sealant, and demonstrated no significant difference between the two groups in operation time, leukocyte count, serum C-reactive protein, and drain bilirubin concentrations.[244] Also, no cases of postoperative bleeding or biliary leakage occurred in either group.[244] Noun *et al.* performed a RCT to compare the use of fibrin glue versus no fibrin glue and found that although postoperative morbidity and mortality were not different between the two groups, the mean total fluid drainage during the three postoperative days and bilirubin concentration were significantly lower in the group with fibrin glue.[245] Figueras *et al.*

performed a RCT to compare fibrin glue application versus no fibrin glue and demonstrated no significant difference in postoperative morbidity, blood loss, blood transfusion, overall drainage volumes, days of postoperative drainage, or incidence of biliary fistula between the two groups.[246] A RCT by Fischer *et al.* compared the use of TachoSil (a fixed combination tissue sealant) versus argon beam coagulator on the cut surface of the liver after hepatectomy, and showed that the mean time to haemostasis was significantly shorter when TachoSil was used compared with argon beam coagulation.[247] Postoperative morbidity and mortality, drainage volume, drainage fluid, and drainage duration did not differ between the two groups.[247]

Each category of interventions has been systematically reviewed previously. A meta-analysis of trials comparing hepatic vascular occlusion versus no vascular occlusion demonstrated no difference in mortality, liver failure, or other morbidities.[66] The blood loss was significantly lower in vascular occlusion compared with no vascular occlusion, but the liver enzymes were significantly elevated in the vascular occlusion group compared with no vascular occlusion.[66] Another meta-analysis compared different techniques for liver parenchymal transection and found significantly fewer infective complications and lower transection blood loss with the clamp-crush method compared to the radiofrequency dissecting sealer.[248] Also, the blood transfusion requirements were significantly lower with the clamp-crush technique compared to CUSA and hydrojet, and the clamp-crush technique was shown to be quicker than CUSA, hydrojet, and the radiofrequency dissecting sealer.[248] A meta-analysis comparing portal triad clamping with other methods of vascular control during liver resection, demonstrated no statistically significant differences in mortality, morbidity, blood transfusion, and length of hospital stay, between portal triad clamping and other forms of vascular control.[249]

No previous review has been conducted to assess and synthesise the comparative effectiveness of specific combinations (i.e. treatment strategies) of interventions during liver resection when used together to decrease operative blood loss and perioperative blood transfusion. Also, there has not been a previous published network meta-analysis. In this review, each combination of interventions was assessed as a treatment strategy, that is, a combination of several interventions. The purpose of this network meta-analysis was to identify the overall treatment effect of a treatment strategy rather than the contribution of each component intervention towards the overall effect. This systematic review is intended as a useful guide for patients and healthcare providers as

they seek to understand the role of different combinations of interventions (treatment strategies) in decreasing blood loss and blood transfusion requirements in people undergoing elective liver resection.

6.1.1. Aims of this review

The overall aim of this network meta-analysis is to identify the best combination of methods (treatment strategy) to decrease blood loss during elective liver resection and to assess the comparative benefits and harms of the different treatment strategies used in order to decrease operative blood loss and perioperative blood transfusion during elective liver resection.

6.2 METHODS

6.2.1 Search strategy

A comprehensive literature search using a combination of free-text terms and controlled vocabulary when applicable was performed of the following databases: MEDLINE, EMBASE, Science Citation Index Expanded, CENTRAL in The Cochrane Library, and World Health Organization International Clinical Trials Registry Platform. The detailed search strategy is provided in Table 6.4. The "related articles" function from PubMed was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed. The references of the identified trials were also searched to identify additional trials for inclusion. Because subsets of all available interventions on this topic have been reviewed comprehensively in existing Cochrane systematic reviews,[66, 248] we also used these reviews as a way to identify trials. No restrictions were made based on language, publication year, or publication status. The latest date for this search was July 16, 2012.

Table 6.4: Detailed search strategy.

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register and Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Wiley)	July 16, 2012	1. Blood loss OR bleeding OR hemorrhage OR haemorrhage OR hemorrhages OR haemorrhages OR hemostasis OR haemostasis OR transfusion 2. MeSH descriptor Hemorrhage explode all trees 3. MeSH descriptor Blood Transfusion explode all trees 4. (#1 OR #2 OR #3) 5. Liver OR hepatic OR hepato* 6. MeSH descriptor Liver explode all trees 7. (5 OR 6) 8. Resection OR resections OR segmentectomy OR segmentectomies 9. (7 AND 8) 10. Hepatectomy OR hepatectomies 11. MeSH descriptor Hepatectomy explode all trees 12. (9 OR 10 OR 11) 13. (4 AND 12)
MEDLINE (PubMed)	January 1947 to July 2012	(Blood loss OR bleeding OR hemorrhage OR haemorrhage OR hemorrhages OR haemorrhages OR hemostasis OR haemostasis OR transfusion OR "Hemorrhage" [MeSH] OR "Blood Transfusion" [MeSH]) AND (((liver OR hepatic OR hepato* OR "liver" [MeSH]) AND (resection OR resections OR segmentectomy OR segmentectomies)) OR hepatectomy OR hepatectomies OR "hepatectomy" [MeSH]) AND ((randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
EMBASE (OvidSP)	Janurary 1974 to July 2012	1. (Blood loss or bleeding or hemorrhage or haemorrhage or hemorrhages or haemorrhages or hemostasis or haemostasis or transfusion).af 2. Exp bleeding/or exp blood transfusion/ 3 .1 or 2 4. (Liver or hepatic or hepato*).af 5. (Resection or resections or segmentectomy or segmentectomies).af 6. 4 and 5 7. (Hepatectomy or hepatectomies).af 8. Exp Liver Resection/ 9. 6 or 7 or 8 10. 3 and 9 11. Exp crossover-procedure/or exp double-blind procedure/or exp randomised controlled trial/or single-blind procedure/ 12. (Random* OR factorial* OR crossover* OR cross over* OR cross-over* OR placebo* OR double* adj blind* OR single* adj blind* OR assign* OR allocat* OR volunteer*).af 13. 11 OR 12

		14. 10 AND 13
Science Citation Index Expanded (http://portal.isiknowledge.com/portal.cgi?DestApp=WOS&Func=Frame)	January 1945 to July 2012	1. TS=(Blood loss OR bleeding OR hemorrhage OR haemorrhage OR hemorrhages OR haemorrhages OR hemostasis OR haemostasis OR transfusion) 2. TS=((liver OR hepatic OR hepato*) AND (resection OR resections OR segmentectomy OR segmentectomies) OR hepatectomy OR hepatectomies) 3. TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) 4. 1 AND 2 AND 3
World Health Organization International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/Default.aspx)	July 2012	Liver resection OR hepatectomy

6.2.2 Inclusion and exclusion criteria

Only RCTs were considered for this network meta-analysis. Studies of other design were excluded because of the risk of bias in such trials and because it is not appropriate to perform network meta-analysis on studies of different study designs as this will make the interpretation more difficult. The participants of the included RCTs underwent elective liver resection using different types of vascular occlusion or no vascular occlusion, different types of parenchymal transection, or different types of management of the liver cut surface, irrespective of the method of vascular occlusion or the nature of the background liver (i.e., normal or cirrhotic). RCTs in which participants underwent liver resection combined with other major surgical procedures (e.g., combined liver and bowel resection for synchronous metastases from colorectal tumours) were excluded.

RCTs that assessed one or more of the following interventions were included in this review:

1. Methods of vascular occlusion (including no vascular occlusion).
2. Methods of liver parenchymal transection.
3. Methods of management of the cut surface (resection plane) of the liver.

The RCTs should clearly state the method of vascular occlusion, method of parenchymal transection, and method of management of the cut surface to be included.

6.2.3 Data extraction

The trials for inclusion were independently identified by two review authors (Constantinos Simillis and Jessica Vaughan) by screening the titles and abstracts. Full text was sought for any references which were identified for potential inclusion by at least one of the authors, and made further selection for inclusion based on the full text. Any discrepancies between the two review authors were resolved through discussion, and if there was still a disagreement between authors, the final decision was taken by a senior co-author.

The following data were independently extracted by the two review authors from each study:

1. First author
2. Year and language of publication
3. Country of conduct of the trial
4. Year(s) in which the trial was conducted
5. Inclusion and exclusion criteria for participants
6. Sample size
7. Participant characteristics such as age, gender, underlying disease, comorbidity, number and proportion of participants with cirrhosis, and number and proportion of participants undergoing major versus minor liver resection.
8. Details of the intervention and treatment strategy that aimed to decrease blood loss and blood transfusion requirements (e.g., surgical technique, procedure and co-intervention, concurrent surgery, and medications).
9. Outcomes (primary outcomes, secondary outcomes).
10. Follow-up time points.
11. Risk of bias

6.2.4 Risk of bias

The risk of bias of the included trials was assessed based on the following bias risk domains: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and vested interest bias. These bias risk domains were chosen based on the advice of The Cochrane Collaboration,[141] the Cochrane Hepato-Biliary Group Module,[209] and reviews published on network meta-analyses.[132] For further details on the individual bias risk domains please review section 5.2.4. For each of these risk domains of bias the studies were categorized as low risk, uncertain risk, and high risk of bias. A trial was considered at low risk of bias if the trial was assessed as at low risk of bias for all domains. Trials with uncertain risk of bias or with high risk of bias for one or more domains were considered trials with high risk of bias.

6.2.5 Outcomes of interest and definitions

The comparative effectiveness of available treatment strategies that aimed to decrease blood loss during liver resection, was assessed for the following outcomes:

Primary outcomes

- Mortality, evaluated both as short term (30-day mortality or in-hospital mortality) and long term (at maximal follow-up).
- Serious adverse events, defined as any event that would increase mortality, is life-threatening, requires inpatient hospitalization, results in a single organ or multi-organ dysfunction, or requires surgical, endoscopic or radiological intervention to treat it. Serious adverse events correspond to Grade III or above of the Clavien-Dindo classification (Table 6.5) and in cases where the authors did not classify the severity of adverse events this classification was followed.[250, 251]
- Quality of life.

Secondary outcomes

- Blood transfusion requirements (proportion of patients requiring red cell or whole blood heterologous blood transfusion, mean quantity of units of blood transfusion).
- Operative blood loss in millilitres (mL).
- Number of participants who had major operative blood loss.
- Operative time in minutes (min).
- Length of hospital stay in days.
- Length of Intensive Therapy Unit (ITU) stay in days.
- Time needed to return to work in days.

Table 6.5: Clavien-Dindo classification of post-operative complications.[250, 251]

Grades	Definitions	Examples
I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions	Drugs such as antiemetics, antipyretics, analgesics, diuretics, and electrolytes; physiotherapy; wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications	Blood transfusions, total parenteral nutrition
III	Requiring surgical, endoscopic or radiological intervention	Bile leak requiring endoscopic stent; reoperation for any cause; drainage of infected intra-abdominal collection
IV	Life-threatening complication requiring high dependency or intensive care management	Dialysis
V	Death of patient	
Suffix d	If the patient suffers from a complication at the time of discharge and needs further follow-up to fully evaluate the complication	

6.2.6 Statistical analysis

For detailed description of the statistical methods used to perform the network meta-analysis please review section 3.2.1. For binary outcomes (mortality, serious adverse events, patients requiring blood transfusion), the OR was calculated. For continuous outcomes (quantity of blood transfused, operative blood loss, hospital stay, ITU stay, operating time), the MD was calculated. A network plot was obtained to ensure that the trials were connected by treatments using Stata/IC 11 (StataCorp LP). Any trials that were not connected to the network were excluded. The network meta-analysis was performed as per the guidance from the NICE DSU documents.[153]

A Bayesian network meta-analysis was conducted using the Markov chain Monte Carlo method in WinBUGS 1.4. The treatment contrast (OR for binary outcomes, MD for continuous outcomes) for any two interventions was modelled as a function of comparisons between each individual intervention and an arbitrarily selected reference group.[152] The reference group in this network meta-analysis was selected on the basis of the 'least intervention', for example, if a treatment group had no vascular occlusion, used finger-fracture or clamp-crush method for parenchymal transection, and no fibrin sealant for dealing with the cut surface, this treatment was used as the reference category. Details of the codes used in WinBUGS 1.4 for the network meta-analyses of binary and continuous outcomes and examples of the binary and continuous 'raw data' inserted into the WinBUGS codes for analysis, are shown in sections 3.3 and 3.4 respectively.

The 95% credible intervals (CrI, similar to 95% confidence intervals in a frequentist method of meta-analysis) were calculated, and the effect estimates and associated 95% CrI for each pairwise comparison were reported in a table. The probability that a treatment ranks as the best treatment for each outcome of interest, was presented in graphs. The cumulative probability of the treatment ranks (i.e. the probability that the treatment is within the top two, the probability that the treatment is within the top three, etc.) was also presented in graphs. In addition, the illustrative risk or absolute proportion of people at risk for an outcome of interest, calculated based on the treatment effects of the network meta-analysis, was presented in tables.

Clinical and methodological heterogeneity was assessed by carefully examining the characteristics and design of included trials. Major sources of clinical heterogeneity included cirrhotic compared to non-cirrhotic livers and major compared to minor liver resections. In addition, considerable heterogeneity was anticipated in the way the intervention was performed. For example, intermittent portal triad clamping may be performed with different time periods of occlusion and non-occlusion. In addition, different doses of fibrin sealant may be used. Different study design and risk of bias may contribute to methodological heterogeneity. Subgroup analysis was not performed because of the paucity of data. The residual deviance and DIC were used for assessing statistically between study heterogeneity as per the guidance from the NICE DSU Technical Support Documents.[153, 252] The between trial SD was also calculated and reported if random-effects model was used.

6.2.7 Treatment strategy

In order to decrease blood loss during elective liver resection, a surgeon may use a particular combination of the different methods of vascular occlusion, of the different methods of parenchymal transection, and of the different methods of dealing with the raw surface of the liver after transection. Therefore, in liver resection, a surgeon typically uses one item from Table 6.1, one item from Table 6.2, and one item from Table 6.3. For example, one surgeon may perform liver resection using intermittent vascular occlusion, clamp crush technique as the method of liver parenchymal transection, and a fibrin sealant on the cut surface; while another surgeon may perform liver resection without using any method of vascular occlusion, with the CUSA as the method of liver parenchymal transection, and without any fibrin sealant on the cut surface. Together, one can consider this combination of one method from each table as a treatment strategy, that is, a combination of several interventions. In terms of network meta-analysis, each unique treatment strategy can be defined as a ’node’. The purpose of this network meta-analysis was to identify the overall treatment effect of a treatment strategy rather than the contribution of each component intervention towards the overall effect.

Not every node was anticipated to be represented in the included trials. Some methods are more commonly practiced than others. From Table 6.1, no vascular occlusion, intermittent portal triad clamping, and continuous portal triad clamping are used more often than other techniques.[66] From Table 6.2, clamp-crush method and CUSA are more commonly applied.[248] The clamp-crush method and the finger-fracture method do not require any special equipment, but the remaining methods do require special equipment. From Table 6.3, common methods of managing cut surface include suturing for large and medium vessels and ducts and performing electrocauterisation of small vessels and ducts.[248] Because of the large number of possible treatment strategies (eight methods of vascular occlusion × six methods of parenchymal transection × four methods of treatment of cut surface, i.e., 192 potential treatment strategies or nodes), a more sparse network graph was constructed based on the treatment strategies used in the trials included. Not all 192 nodes were expected to be represented in the trials available in the literature.

Because of the few trials that could be included for network meta-analysis in this review, the treatments were revised into fewer categories by having only three methods of vascular occlusion (no vascular occlusion, continuous vascular occlusion, or intermittent vascular occlusion) and by having only two methods of treatment of cut surface (fibrin sealant used or no fibrin sealant used). The allocated treatment codes and the revised categories of vascular occlusion, method of parenchymal transection, and dealing with the cut surface are shown in Table 6.6. This reduced the categories to 36 treatment strategies or nodes (three methods of vascular occlusion × six methods of parenchymal transection × two methods of treatment of cut surface).

Table 6.6: Allocated treatment codes and different categories of vascular occlusion, parenchymal transection, and methods of dealing with raw surface used in this review.

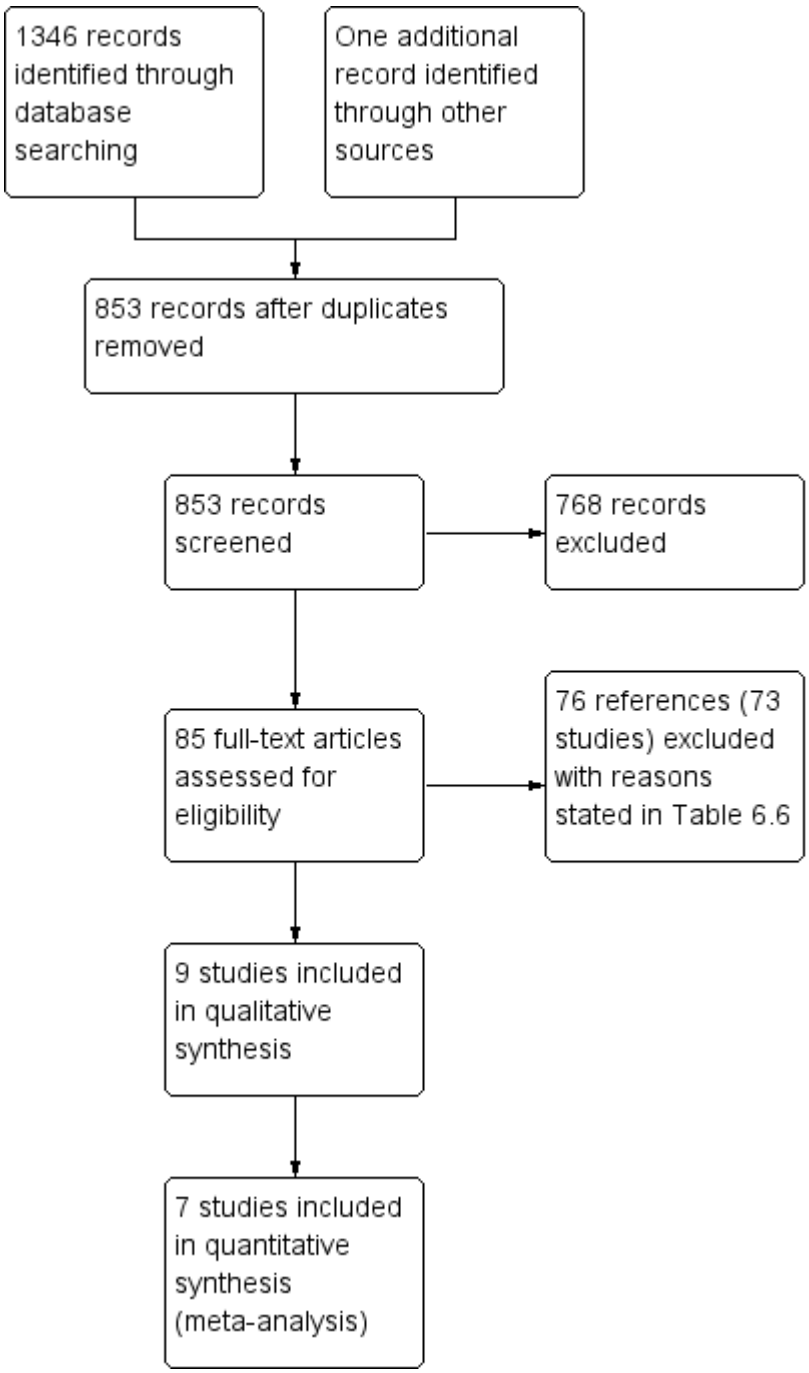
Vascular occlusion
No vascular occlusion (V1)
Continuous vascular occlusion (V2)
Intermittent vascular occlusion (V3)
Parenchymal transection
Finger-fracture method (P1)
Clamp-crush method (P2)
Cavitron ultrasonic surgical aspirator (CUSA) (P3)
Sharp dissection (P4)
Radiofrequency dissecting sealer (P5)
Ultrasonic shears (P6)
Methods of dealing with raw surface
No fibrin sealant used (R1)
Fibrin sealant used (R2)

6.3 RESULTS

6.3.1 Eligible studies

A total of 1347 references were identified through electronic searches of CENTRAL (n=170), MEDLINE (n=370), EMBASE (n=442), Science Citation Index Expanded (n=364), and RCTs registers (n=1). Four hundred and ninety four duplicates between databases were excluded. A further 768 clearly irrelevant references were excluded through screening titles and reading abstracts. Eighty five references were retrieved for further assessment. No more references were identified through scanning reference lists of the identified randomised trials. Seventy six references (73 studies) were excluded after reviewing the studies in detail, for the reasons listed under Table 6.6. For inclusion, a trial should have given a clear definition of the method used for vascular occlusion (including no vascular occlusion), transection method, and method of managing the liver cut surface. In total, nine references of nine completed RCTs met the inclusion criteria.[29, 242, 253-259]

Figure 6.2: Study flow diagram.



6.3.2 Excluded studies

Seventy six references (73 studies) were excluded after reviewing the studies in detail, for the reasons listed under Table 6.7. Of the 73 studies excluded, 24 studies were excluded because they were not RCTs.[240, 260-282] One report was the protocol of a trial.[283] Seven trials did not compare different methods of vascular occlusion or parenchymal transection or method of management of cut surface.[284-290] One trial included participants undergoing liver resection along with other major procedures.[246] Four trials compared variations of methods of vascular occlusion that would have been classified under the same treatment categories included in this review.[237, 239, 291, 292] The remaining 36 trials included comparisons of one aspect of different methods of vascular occlusion or parenchymal transection or management of cut surface. However, one or more aspects of methods of vascular occlusion or parenchymal transection or management of cut surface not being compared were either not stated or were chosen in a non-random manner. Therefore, these trials were excluded.[67, 70, 243, 245, 247, 253, 293-322]

Table 6.7: Reasons for excluded studies.

Study	Reason for exclusion
Aldrighetti 2006 [260]	Not a randomised clinical trial
Arita 2005 [293]	Two methods of vascular occlusion used, separate data not reported
Belghiti 1996 [253]	Two methods of parenchymal transection used, separate data unavailable
Campagnacci 2007 [294]	Methods of management of raw surface not reported
Capussotti 2012 [295]	Separate data for method of vascular occlusion not clearly reported (intermittent pringle manouvre was used only in case of significant bleeding)
Chapman 2000 [296, 323]	Methods of vascular occlusion and parenchymal transection not reported
Chapman 2007 [297]	Methods of vascular occlusion and parenchymal transection not reported
Chau 2005 [261]	Not a randomised clinical trial
Chen 2006 [291]	Compares different variations of vascular occlusion which will fall under the same category of vascular occlusion in our review
Cherqui 1999 [262]	Not a randomised clinical trial
Chiappa 2007 [263]	Not a randomised clinical trial
Chouker 2004 [67]	Methods of parenchymal transection and management of raw surface not reported
Cresswell 2009 [264]	Not a randomised clinical trial
Dello 2011 [298, 324]	Methods of parenchymal transection and raw surface management not reported
El-Kharboutly 2004 [299]	Methods of vascular occlusion and parenchymal transection not reported
El-Moghazy 2009 [300]	Method of raw surface management not included in methods of dealing with raw surface in our review protocol
Esaki 2006 [301]	Method of management of raw surface not reported
Felekouras 2006[265]	Not a randomised clinical trial
Figueras 2003 [303]	Two methods of parenchymal transection used, separate data not reported
Figueras 2005 [302]	Method of parenchymal transection not reported
Figueras 2007 [246]	Patients underwent liver resections combined with other major surgical procedures
Fischer 2011 [247]	Methods of parenchymal transection and method of vascular occlusion not reported
Frilling 2005 [70]	Separate data for method of vascular occlusion not clearly reported (in some cases the Pringle manoeuvre was used). Method of parenchymal transection not reported
Fu 2010 [266]	Not a randomised clinical trial
Gugenheim 2011 [304]	Method of vascular occlusion not reported
Guo 2010 [284]	Not comparing methods of vascular occlusion or parenchymal transection or raw surface

Hasegawa 2002 [285]	Not comparing methods of vascular occlusion or parenchymal transection or raw surface
Hashimoto 2007 [286]	Not comparing methods of vascular occlusion or parenchymal transection or raw surface
Ikeda 2009 [305]	Two methods of vascular occlusion used, separate data not available
Izzo 2008 [306]	Multiple methods of parenchymal transection used, separate data unavailable
Johnson 1998 [267]	Not a randomised clinical trial
Kato 2008 [287]	Not comparing methods of vascular occlusion or parenchymal transection or raw surface
Kim 2007 [268]	Not a randomised clinical trial
Kim 2008 [307]	Method of raw surface management not included in methods of dealing with raw surface in our review protocol
Kohno 1992 [308]	Method of vascular occlusion not reported
Koo 2005 [309]	Method of raw surface management not reported
Lentschener 1997 [288, 325]	Not comparing methods of vascular occlusion or parenchymal transection or raw surface
Liang 2009 [310]	Method of parenchymal transection and management of raw surface not reported
Liu 1993 [326]	No report on method of vascular occlusion and method of parenchymal transection
Lodge 2005 [311]	Not comparing methods of vascular occlusion or parenchymal transection or raw surface
Man 1997 [312]	Method of parenchymal transection and management of raw surface not reported
Man 2002 [269]	Not a randomised clinical trial
Man 2003 [313]	Management of raw surface not reported
Matot 2002 [289]	Not comparing methods of vascular occlusion, parenchymal transection or management of raw surface
Mirza 2011 [314]	Method of vascular occlusion and method of parenchymal transection not reported
Nagano 2005 [270]	Not a randomised clinical trial
Noritomi 2005 [271]	Not a randomised clinical trial
Noun 1996 [245]	Two methods of vascular occlusion and parenchymal transection used. Separate data not available
Palibrk 2012 [272]	Not a randomised clinical trial
Pietsch 2010 [273]	Not a randomised clinical trial
Rahbari 2009 [283]	Protocol only
Rahbari 2011 [327]	Two methods of parenchymal transection used, separate data unavailable
Rau 1995 [274]	Not a randomised clinical trial
Richter 2009 [243]	Method of vascular occlusion not reported
Saiura 2006 [316]	Method of raw surface management not included in methods of dealing with raw surface in our review protocol
Scatton 2011 [317]	Method of parenchymal transection was left to surgeons discretion

Schmidt 2008 [318]	Parenchymal transection performed according to surgeon's preference and local standards. Separate data not reported
Schwartz 2004 [319]	Method of parenchymal transection not reported
Shimada 1994 [275]	Not a randomised clinical trial
Si-Yuan 2011 [328]	Compares different variations of vascular occlusion which will fall under the same category of vascular occlusion in our review
Smyrniotis 2002 [277]	Quasi-randomised (random sequence generated by hospital number). This was discovered following correspondence with authors when it was included in a previous review
Smyrniotis 2003 [276]	Quasi-randomised (random sequence generated by hospital number)
Sugo 2005 [278]	Not a randomised clinical trial
Takayama 2001 [320]	Two methods of vascular occlusion used, separate data unavailable
Taniguchi 1992 [279]	Not a randomised clinical trial
Van Den Broek 2011 [239]	Compares different variations of vascular occlusion which will fall under the same category of vascular occlusion in our review
Wang 2006 [321]	Methods of vascular occlusion or parenchymal transection or raw surface not reported
Wang 2011 [240]	Not a randomised clinical trial
Wong 2003 [322]	Methods of parenchymal transection and management of raw surface not reported
Wu 2002 [292]	Compares different variations of vascular occlusion which will fall under the same category of vascular occlusion in our review
Wu 2006 [280]	Not a randomised clinical trial
Xia 2008 [281]	Not a randomised clinical trial
Yao 2006 [290]	Not comparing methods of vascular occlusion or parenchymal transection or raw surface
Yokoo 2012 [282]	Not a randomised clinical trial

6.3.3 Characteristics of the included studies

As discussed in the methodology section of this chapter (section 6.2.7), in order to decrease blood loss during elective liver resection, a surgeon may use a particular combination of the different methods of vascular occlusion, of the different methods of parenchymal transection, and of the different methods of dealing with the raw surface of the liver after transection. Together, one can consider this combination as a treatment strategy, that is, a combination of several interventions. Because of the few trials that could be included for network meta-analysis in this review, the treatments were revised into fewer categories by having only three methods of vascular occlusion (no vascular occlusion, continuous vascular occlusion, or intermittent vascular occlusion) and by having only two methods of treatment of cut surface (fibrin sealant used or no fibrin sealant used). The allocated treatment codes and the revised categories of vascular occlusion, method of parenchymal transection, and dealing with the cut surface are shown in Table 6.6.

The individual characteristics and the treatments used in each of the nine RCTs included in this network meta-analysis are shown in Tables 6.8 to 6.16. All the included trials assessed different methods of open liver resection by using different combinations of vascular occlusion, parenchymal transection, and management of the liver cut surface, in order to decrease blood loss during liver resection. Seven trials were two-arm trials.[29, 254, 256-259, 329] There was one three-arm trial,[242] and one four-arm trial.[255] However, one arm in each of the latter two trials was excluded because the methods of parenchymal transection used in these trials (parenchymal transection using bipolar cautery and water jet, respectively) were not included in this review.[242, 255]

Eleven different treatment strategies out of 36 possible treatment strategies were used in the trials included in this review. A total of 617 participants were randomised to the 11 different treatment strategies in these trials. However, four treatment strategies in two trials were not connected to the network in any of the outcomes (i.e. they were not compared directly with any of the other treatment strategies for any of the outcomes of interest).[254, 329] Thus, 496 participants were included in the network meta-analysis, randomised to seven different treatment strategies in the seven trials that contributed data for the network meta-analysis.[29, 242, 255-259] A summary of the treatments used and types of participants included in all the included studies is shown in Table 6.17.

Table 6.8: Characteristics of study by Belghiti *et al.*[329]

Methods	Randomised clinical trial
Participants	Country: France. Number randomised: 86. Post-randomisation drop-outs: 0 (0%). Revised sample size: 86. Average age: 51 years. Females: 39 (45.3%). Major hepatic resection: 39 (45.3%). Cirrhosis: 25 (29.1%) Inclusion criteria 1. Elective resection. 2. Total vascular exclusion not required. 3. No bilioenteric anastomosis. 4. No associated gastrointestinal procedures.
Interventions	Participants were randomly assigned to two groups. Group 1: Intermittent vascular occlusion with cavitron ultrasonic surgical aspirator (CUSA) and fibrin sealant (n = 44). Group 2: Continuous vascular occlusion with CUSA and fibrin sealant (n = 42).
Outcomes	The outcomes reported were peri-operative mortality, morbidity, blood loss, blood transfusion requirements, and hospital stay.

Table 6.9: Characteristics of study by Capusotti (2003) *et al.*[254]

Methods	Randomised clinical trial
Participants	Country: Italy. Number randomised: 35. Post-randomisation drop-outs: 0 (0%). Revised sample size: 35. Average age: 63 years. Females: 8 (22.9%). Major hepatic resection: 8 (22.9%). Cirrhosis: 35 (100%) Inclusion criteria 1. < 75 years. 2. HCC. 3. Cirrhotic. 4. Child A.
Interventions	Participants were randomly assigned to two groups. Group 1: Intermittent vascular occlusion with clamp-crush and fibrin sealant (n = 18). Group 2: Continuous vascular occlusion with clamp-crush and fibrin sealant (n = 17).
Outcomes	The outcomes reported were peri-operative mortality, morbidity, blood loss, blood transfusion requirements, and operating time.

Table 6.10: Characteristics of study by Capusotti (2006) *et al.*[29]

Methods	Randomised clinical trial
Participants	Country: Italy. Number randomised: 126. Post-randomisation drop-outs: 0 (0%). Revised sample size: 126. Average age: 51 years. Females: 51 (40.5%). Major hepatic resection: 56 (44.4%). Cirrhosis: 19 (15.1%) Inclusion criteria 1. Hepatic resection. 2. Resectable tumour on intraoperative ultrasound. 3. No concomitant bowel or bile duct resection. 4. No total vascular exclusion
Interventions	Participants were randomly assigned to two groups. Group 1: Intermittent vascular occlusion with clamp-crush and no fibrin sealant (n = 63). Group 2: No vascular occlusion with clamp-crush and no fibrin sealant (n = 63).
Outcomes	The outcomes reported were peri-operative mortality, morbidity, blood loss, blood transfusion requirements, and hospital stay.

Table 6.11: Characteristics of study by Doklestic *et al.*[242]

Methods	Randomised clinical trial
Participants	Country: Serbia. Number randomised: 40. Post-randomisation drop-outs: not stated. Revised sample size: 40. Average age: 59 years. Females: 27 (67.5%). Major hepatic resection: 20 (50.0%). Cirrhosis: 0 (0%). Inclusion criteria Patients undergoing liver resection. Exclusion criteria 1. Liver cirrhosis.
Interventions	Participants were randomly assigned to two groups. Group 1: Intermittent vascular occlusion with CUSA and no fibrin sealant (n = 20). Group 2: Continuous vascular occlusion with clamp-crush and no fibrin sealant (n = 20).
Outcomes	The outcomes reported were mortality, operating time, blood loss, transfusion requirements, and hospital stay.
Notes	Another group in which liver resection was performed using bipolar cautery was not included in the review since this was not a method of parenchymal transection that we included in this review.

Table 6.12: Characteristics of study by Lesurtel *et al.*[255]

Methods	Randomised clinical trial
Participants	Country: Switzerland. Number randomised: 75. Post-randomisation drop-outs: not stated. Revised sample size: 75. Average age: 55 years. Females: 38 (50.7%). Major hepatic resection: 42 (56.0%). Cirrhosis: 0 (0%). Inclusion criteria 1. More than 2 segments. 2. Tumours 3. Platelet count > 100000/ml. 4. Prothrombin activity >60%. Exclusion criteria 1. Cirrhotic. 2. Cholestatic (serum bilirubin > 100 mumol/L).
Interventions	Participants were randomly assigned to two groups. Group 1: No vascular occlusion with CUSA and no fibrin sealant (n = 25). Group 2: No vascular occlusion with dissecting sealer and no fibrin sealant (n = 25). Group 3: Vascular occlusion with clamp-crush and no fibrin sealant (n = 25).
Outcomes	The outcomes reported were mortality, serious adverse events, hospital stay, transfusion requirements, and blood loss.
Notes	Another group in which parenchymal transection was performed using water jet was excluded since this was not one of the parenchymal transection methods assessed in this review.

Table 6.13: Characteristics of study by Lupo *et al.*[256]

Methods	Randomised clinical trial
Participants	Country: Italy. Number randomised: 51. Post-randomisation drop-outs: 1 (2%). Revised sample size: 50. Average age: 62 years. Females: 14 (28%). Major hepatic resection: 21 (42.0%) Cirrhosis: 7 (14.0%) Inclusion criteria
Interventions	Participants were randomly assigned to two groups. Group 1: No vascular occlusion with radiofrequency dissecting sealer and no fibrin sealant (n = 24). Group 2: No vascular occlusion with clamp-crush and no fibrin sealant (n = 26).
Outcomes	The outcomes reported were mortality, serious adverse events, and transfusion requirements.

Table 6.14: Characteristics of study by Park *et al.*[257]

Methods	Randomised clinical trial
Participants	Country: Korea. Number randomised: 50. Post-randomisation drop-outs: not stated. Revised sample size: 50. Average age: 31 years. Females: 11 (22%). Major hepatic resection: not stated Cirrhosis: not stated Inclusion criteria 1. Age >18 years. Exclusion criteria 1. The recipient had experienced fulminant hepatic failure. 2. The graft-to-recipient body weight ratio (GRWR) was <0.9%. 3. A frozen biopsy sample from the donor liver showed >30% macrovesicular steatosis before donor hemihepatectomy. 4. The transplant was ABO-incompatible. 5. The recipient had previously undergone organ transplantation. 6 Recipient had undergone or was scheduled to undergo multiorgan transplantation.
Interventions	Participants were randomly assigned to two groups. Group 1: Intermittent vascular occlusion with CUSA and no fibrin sealant (n = 25). Group 2: No vascular occlusion with CUSA and no fibrin sealant (n = 25).
Outcomes	The outcomes reported were mortality, operating time, blood loss, and hospital stay.

Table 6.15: Characteristics of study by Petrowsky *et al.*[258]

Methods	Randomised clinical trial
Participants	Country: Switzerland. Number randomised: 73. Post-randomisation drop-outs: not stated. Revised sample size: 73. Average age: 57 years. Females: 35 (47.9%). Major hepatic resection: 73 (100%). Cirrhosis: 0 (0%) Inclusion criteria 1. Major hepatectomies. 2. No cirrhosis
Interventions	Participants were randomly assigned to two groups. Group 1: Intermittent vascular occlusion with clamp-crush and no fibrin sealant (n = 36). Group 2: Continuous vascular occlusion with clamp-crush and no fibrin sealant (n = 37).
Outcomes	The outcomes reported were mortality, serious adverse events, hospital stay, transfusion requirements, blood loss and operating time.

Table 6.16: Characteristics of study by Smyrniotis *et al.*[259]

Methods	Randomised clinical trial
Participants	Country: Greece Number randomised: 82 Post-randomisation drop-outs: not stated Revised sample size: 82 Average age: 63 years Females: 17 (20.7%) Major hepatic resection: 60 (73.2%) Cirrhosis: 12 (14.6%) Inclusion criteria
Interventions	Participants were randomly assigned to two groups. Group 1: Continuous vascular occlusion with sharp dissection and no fibrin sealant (n = 41). Group 2: Continuous vascular occlusion with clamp-crush and no fibrin sealant (n = 41).
Outcomes	The outcomes reported were mortality, serious adverse events, transfusion requirements, hospital stay, operating time, and blood loss.

Table 6.17: Summary of treatments used and types of participants included in all the included studies.

Study	Vascular occlusion	Parenchymal transection	Liver raw surface	Codes of the comparisons	Number of participants	Major liver resections	Cirrhosis
Belghiti 1999	intermittent vascular occlusion versus continuous vascular occlusion	cavitron ultrasonic surgical aspirator (CUSA)	fibrin sealant	V3P3R2 versus V2P3R2	86	39 (45.3%)	25 (29.1%)
Capussotti 2003	intermittent vascular occlusion versus continuous vascular occlusion	clamp-crush	fibrin sealant	V3P2R2 versus V2P2R2	35	8 (22.9%)	35 (100%)
Capussotti 2006	intermittent vascular occlusion versus no vascular occlusion	clamp-crush	no fibrin sealant	V3P2R1 versus V1P2R1	126	56 (44.4%)	19 (15.1%)
Doklestic 2012	intermittent vascular occlusion	CUSA versus clamp-crush	no fibrin sealant	V3P3R1 versus V3P2R1	40	20 (50.0%)	0 (0%)
Lesurtel 2005	no vascular occlusion versus no vascular occlusion versus continuous vascular occlusion	CUSA versus radiofrequency dissecting sealer versus clamp-crush method	no fibrin sealant	V1P3R1 versus V1P5R1 versus V2P2R1	75	42 (56.0%)	0 (0%)
Lupo 2007	no vascular occlusion	radiofrequency dissecting sealer versus clamp-crush	no fibrin sealant	V1P5R1 versus V1P2R1	50	21 (42.0%)	7 (14.0%)
Park 2012	intermittent vascular occlusion versus no vascular occlusion	CUSA	no fibrin sealant	V3P3R1 versus V1P3R1	50	Not stated	Not stated
Petrowsky 2006	intermittent vascular occlusion versus continuous vascular occlusion	clamp-crush	no fibrin sealant	V3P2R1 versus V2P2R1	73	73 (100%)	0 (0%)
Smyrniotis 2005	continuous vascular occlusion	sharp dissection versus clamp-crush	no fibrin sealant	V2P4R1 versus V2P2R1	82	60 (73.2%)	12 (14.6%)

Footnotes for Table 6.17: Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin, V1P3R1=no vascular occlusion with CUSA and no fibrin, V1P5R1= no vascular occlusion with radiofrequency dissecting sealer and no fibrin, V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin, V2P2R2= continuous vascular occlusion with clamp-crush and fibrin, V2P3R2=continuous vascular occlusion with CUSA and fibrin, V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin, V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin, V3P3R1=intermittent vascular occlusion with CUSA and no fibrin, V3P2R2= intermittent vascular occlusion with clamp-crush and fibrin, V3P3R2=intermittent vascular occlusion with CUSA and fibrin.

The quality of the liver and the type of hepatectomy can influence the outcome of liver resection. Table 6.18 shows the seven treatment strategies included in the network meta-analysis and the number of participants included in each strategy, along with the proportion of major resections performed and cirrhotic livers included in each treatment strategy. Major liver resection was defined as a right or left hemihepatectomy (or lobectomy), or extended hemihepatectomy (or extended lobectomy), or resection of three or more liver segments.

Table 6.18: Summary of the seven treatment strategies included in the network meta-analysis and the number of participants included in each strategy, along with the proportion of major resections performed and cirrhotic livers included in each treatment strategy.

Treatment strategy	Total number of participants	Major resections performed	Cirrhotic livers included
V1P2R1	89	41 (46.1%)	6 (6.7%)
V1P3R1	50	13 out of 25 reported (52%)	0 out of 25 reported (0%)
V1P5R1	49	24 (49.0%)	3 (6.1%)
V2P2R1	103	84 (81.6%)	6 (5.8%)
V2P4R1	41	29 (70.7%)	6 (14.6%)
V3P2R1	119	71 (59.7%)	6 (5.0%)
V3P3R1	45	10 out of 20 reported (50.0%)	0 out of 20 reported (0%)
Overall	**496**	**272 out of 446 reported (61.0%)**	**38 out of 446 reported (8.5%)**

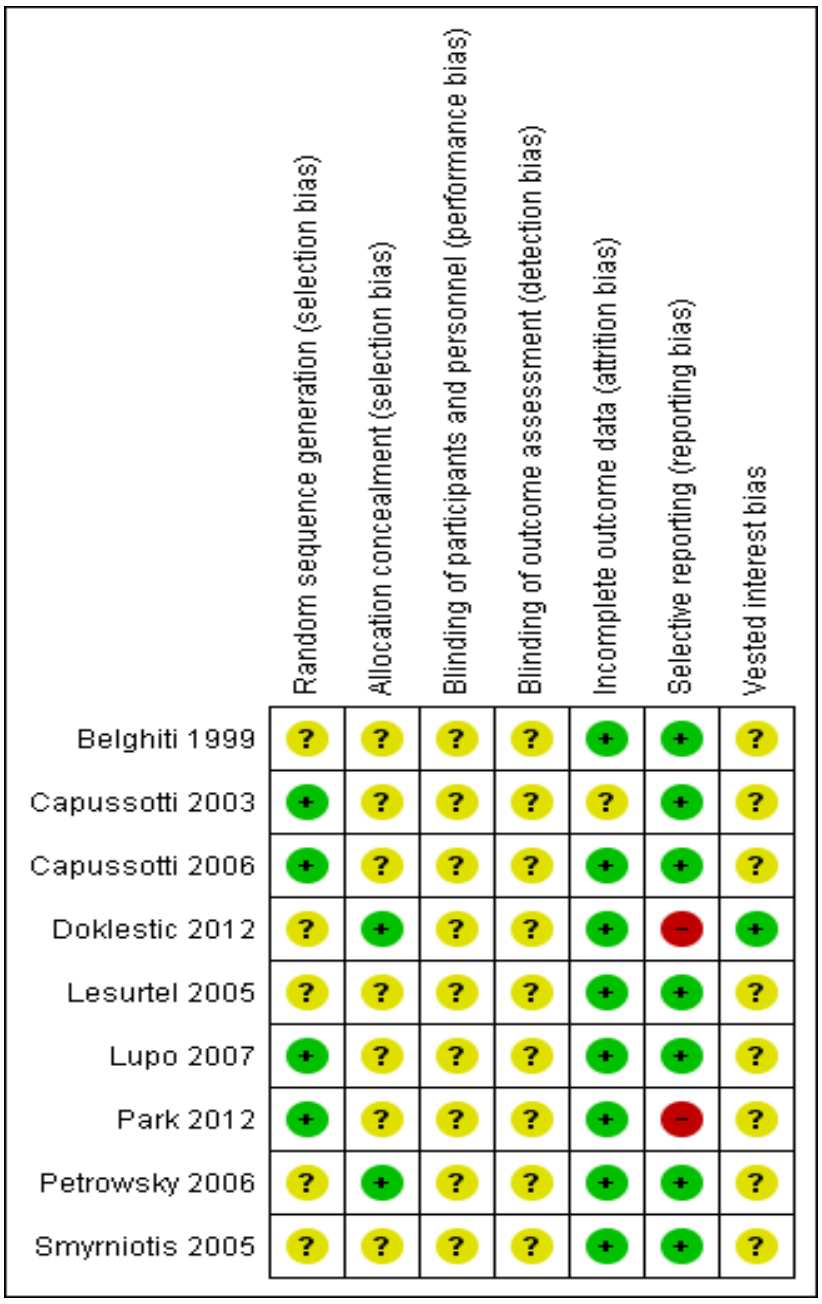
Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin, V1P3R1=no vascular occlusion with CUSA and no fibrin, V1P5R1= no vascular occlusion with radiofrequency dissecting sealer and no fibrin, V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin, V2P4R1= continuous vascular occlusion with sharp dissection and no fibrin, V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin, V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

6.3.4 Risk of bias in included studies

The risk of bias in the included trials is summarised in Figure 6.3 and Figure 6.4. All trials were at high risk of bias. The risk of bias of the included trials was assessed for the following domains:

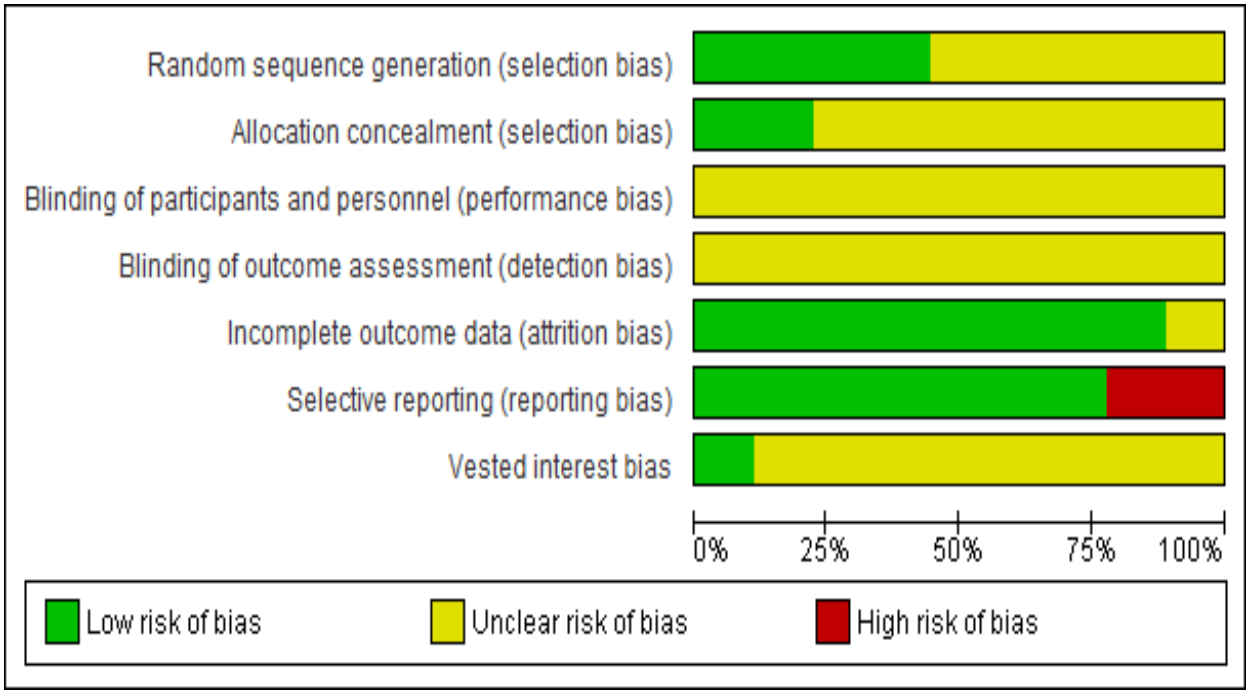
- **Allocation:** Four trials (44%) had adequate sequence generation.[29, 254, 256, 257] Two trials (22%) had adequate allocation concealment.[242, 258] Thus, no trials (0%) had low risk of bias due to allocation.
- **Blinding:** None of the trials reported any blinding.
- **Incomplete outcome data:** Eight of the nine trials (89%) were free from bias due to incomplete outcome data.[29, 242, 255-259, 329]
- **Selective reporting:** Seven trials (78%) reported mortality and serious adverse events and hence were considered to be free from bias.[29, 254-256, 258, 259, 329]
- **Other potential sources of bias:** Only one trial reported the source of funding and the vested interest bias was rated to be low in this trial.[242] The remaining trials were at unclear risk of bias.

Figure 6.3: Risk of bias summary - review authors' judgments about each risk of bias item for each included study.



Footnotes: green plus sign = low risk of bias, yellow question mark = unclear risk of bias, red minus sign = high risk of bias.

Figure 6.4: Risk of bias graph - review authors' judgments about each risk of bias item presented as percentages across all included studies.

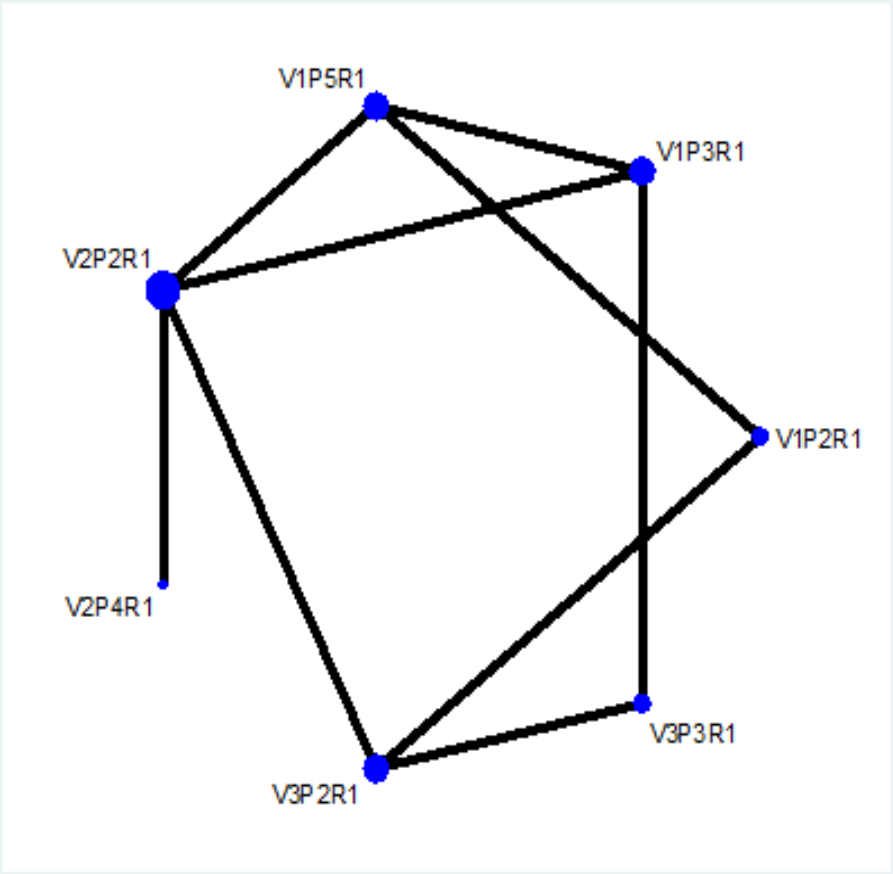


6.3.5 Overall results of network meta-analysis

6.3.5.1. Mortality

All the seven trials (496 participants) provided data for the network meta-analysis on short-term mortality.[29, 242, 255-259] There were seven deaths in the included studies giving an overall mortality of 1.4%. The network plot for this outcome is shown in Figure 6.5. The results and model-fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model is provided in Table 6.18. The between-study standard deviation (tau) was 0.60. As indicated in Table 6.19, the fixed-effect model was preferred based on the DIC statistics. There was no evidence of inconsistency in the network. The pairwise ORs for the different treatment comparisons are shown in Table 6.20. As shown in Table 6.20, there was no evidence of any significant difference in mortality between the different treatments. The absolute proportion of people with mortality based on an illustrative risk of 3.5%[330] is shown in the summary of findings for this outcome in Table 6.21. As shown in Figure 6.6, none of the treatment strategies ranked best with more than 90% probability. Also, none of the treatment strategies ranked worst with more than 90% probability. As shown in Figure 6.7, there is more than 90% probability that V3P3R1 (intermittent vascular occlusion with CUSA and no fibrin) is within the five best treatments (of seven treatments). All the remaining treatments other than V2P4R1 (continuous vascular occlusion with sharp dissection and no fibrin) are within the six best treatments. There is substantial uncertainty about the treatment strategy with the lowest or highest mortality.

Figure 6.5: Network plot of the treatment strategies for the outcome mortality.



Footnotes: circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Table 6.19: Results and model fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model for the outcome mortality.

	Fixed-effect model	Random-effects model	Inconsistency model (random-effects)
d[2]	1.92 (95% CI -2.29 to 6.13)	1.7 (95% CI -5.33 to 8.73)	-
d[3]	-0.18 (95% CI -4.2 to 3.84)	-0.21 (95% CI -6.29 to 5.88)	-
d[4]	0.6 (95% CI -3.29 to 4.5)	0.6 (95% CI -6.08 to 7.27)	-
d[5]	0.6 (95% CI -6.68 to 7.89)	0.62 (95% CI -9.85 to 11.09)	-
d[6]	0.09 (95% CI -2.99 to 3.18)	0.16 (95% CI -5.25 to 5.58)	-
d[7]	-1.23 (95% CI -5.45 to 2.98)	-0.89 (95% CI -8.12 to 6.33)	-
Dbar	42.93	42.82	44.28
pD	11.07	11.68	12.06
DIC	54	54.49	56.35

Footnotes: d[2] indicates the log odds ratio between treatment 2 and treatment 1, d[3] indicates the log odds ratio between treatment 3 and treatment 1, etc.; Dbar indicates the posterior mean of the residual deviance; pD indicates the effective number of parameters (leverage); DIC indicates the 'Deviance Information Criterion'. A lower Dbar indicates a better model fit. However, a model with lower DIC is generally chosen to aid better interpretation as it takes the model complexity into account. A lower DIC indicates a better model fit. Differences of less than 3 to 5 between the models are not considered important. Based on the information, fixed-effect model is the preferred model. There is no evidence of inconsistency since the difference in DIC between consistency and inconsistency models was not significant.

Table 6.20: Pairwise odds ratios of the different treatment comparisons for the outcome mortality. There was no statistically significant difference between the treatment strategies for the outcome mortality.

	V1P3R1	**V1P5R1**	**V2P2R1**	**V2P4R1**	**V3P2R1**	**V3P3R1**
V1P2R1	OR 6.83; 95% CI 0.1 to 459.49	OR 0.84; 95% CI 0.02 to 46.5	OR 1.83; 95% CI 0.04 to 89.57	OR 1.83; 95% CI 0 to 2660.48	OR 1.1; 95% CI 0.05 to 23.98	OR 0.29; 95% CI 0 to 19.67
V1P3R1	-	OR 0.12; 95% CI 0 to 41.17	OR 0.27; 95% CI 0 to 82.55	OR 0.27; 95% CI 0 to 1202.95	OR 0.16; 95% CI 0 to 29.61	OR 0.04; 95% CI 0 to 16.43
V1P5R1	-	-	OR 2.19; 95% CI 0.01 to 587.54	OR 2.18; 95% CI 0 to 8952.18	OR 1.31; 95% CI 0.01 to 207.83	OR 0.35; 95% CI 0 to 117.53
V2P2R1	-	-	-	OR 1; 95% CI 0 to 3850.15	OR 0.6; 95% CI 0 to 85.91	OR 0.16; 95% CI 0 to 49.23
V2P4R1	-	-	-	-	OR 0.6; 95% CI 0 to 1634.74	OR 0.16; 95% CI 0 to 718.88
V3P2R1	-	-	-	-	-	OR 0.27; 95% CI 0 to 49.19

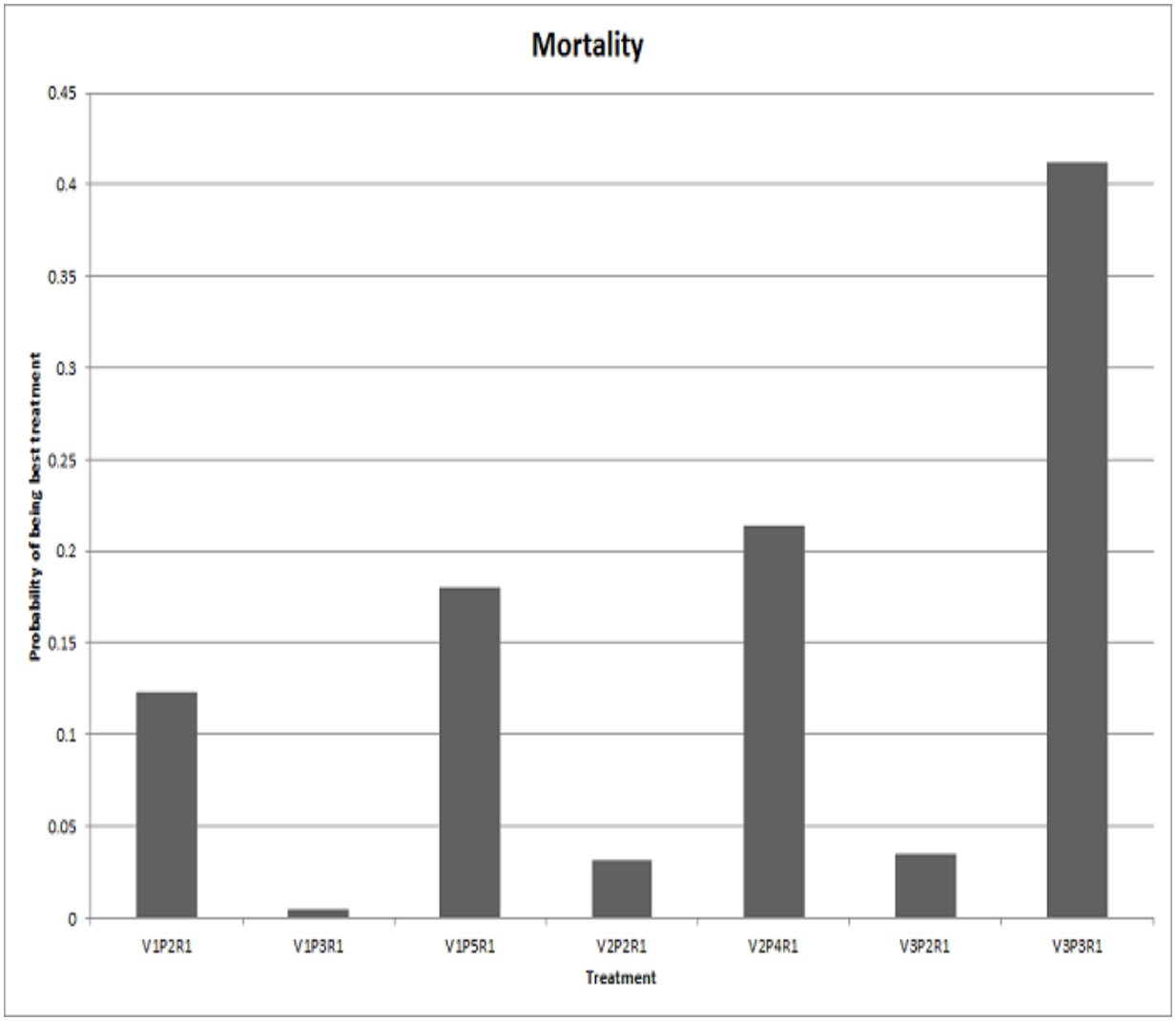
Footnotes: OR=odds ratio; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Table 6.21: Summary of findings for the outcome mortality, including: quality of evidence, treatment strategies compared, the treatment effect for each treatment strategy from the network meta-analysis performed, and the corresponding illustrative risk for each treatment strategy.

Methods to decrease blood loss during liver resection (mortality)		
Patient or population: people undergoing open liver resection **Settings:** secondary or tertiary **Intervention and control:** various treatments		
Number of trials (participants)	7 trials (496 participants)	
Overall quality of evidence	Very low i.e. we are very uncertain about the estimate	
Groups	**Illustrative risk**	**Treatment effect**
Assumed risk in control group (V1P2R1)*	35 per 1000	-
Corresponding risk in V1P3R1	199 per 1000 (4 to 943)	OR 6.83 (95% CI 0.1 to 459.49)
Corresponding risk in V1P5R1	30 per 1000 (1 to 628)	OR 0.84 (95% CI 0.02 to 46.5)
Corresponding risk in V2P2R1	62 per 1000 (1 to 765)	OR 1.83 (95% CI 0.04 to 89.57)
Corresponding risk in V2P4R1	62 per 1000 (0 to 1000)	OR 1.83 (95% CI 0 to 2660.48)
Corresponding risk in V3P2R1	38 per 1000 (2 to 465)	OR 1.1 (95% CI 0.05 to 23.98)
Corresponding risk in V3P3R1	10 per 1000 (0 to 416)	OR 0.29 (95% CI 0 to 19.67)
*The basis for the **assumed risk** was from literature. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).		

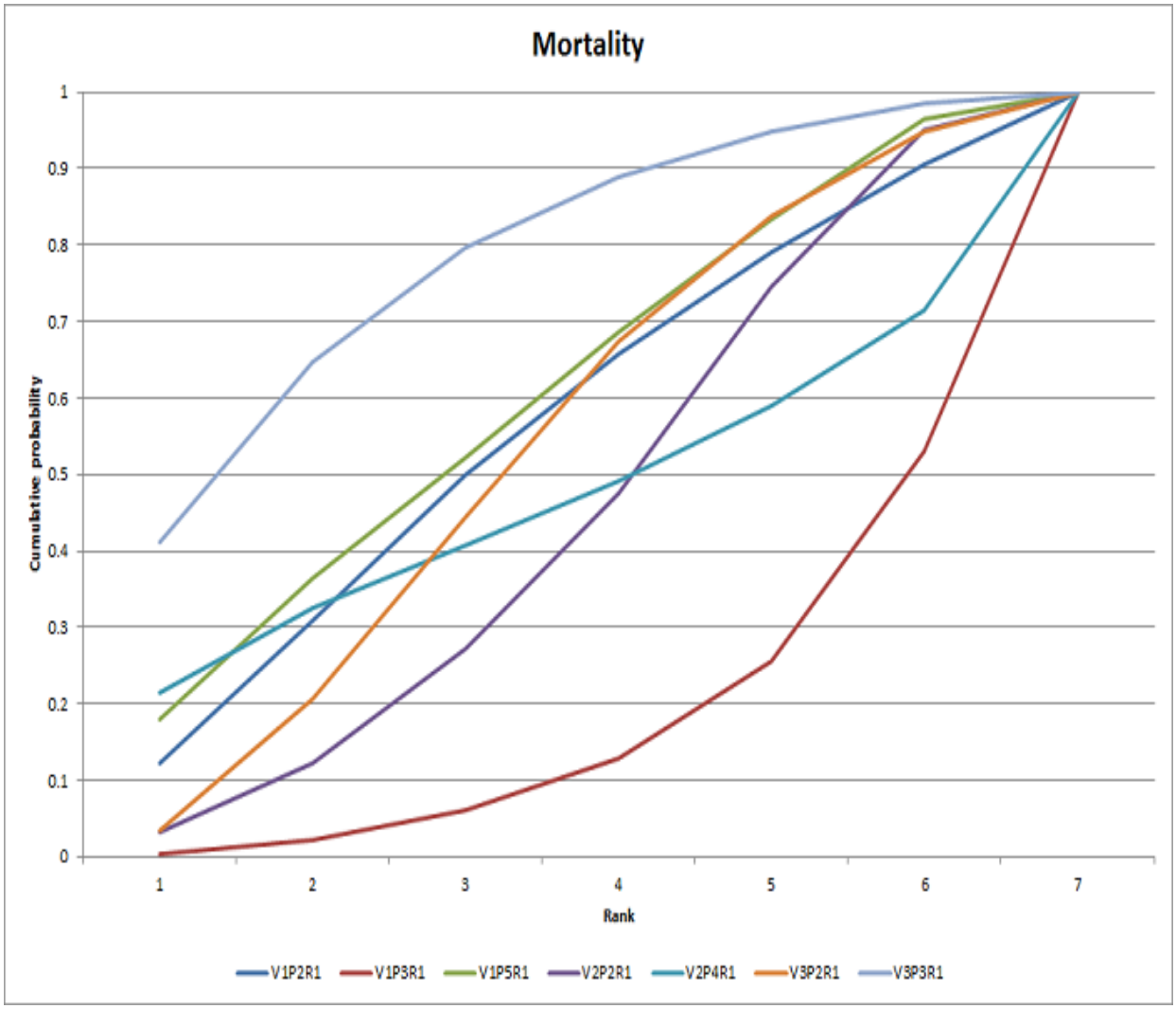
Footnotes: OR=odds ratio; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.6: Probability of being best treatment strategy for the outcome mortality. None of the treatment strategies ranked best with more than 90% probability, and there is a lot of uncertainty about the treatment strategy with the lowest mortality.



Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.7: Cumulative probability of ranks of different treatment strategies for the outcome mortality. There is more than 90% probability that V3P3R1 is within the five best treatments (of seven treatments). All the remaining treatments other than V2P4R1 are within the six best treatments. There is substantial uncertainty about the treatment strategy with the lowest or highest mortality.

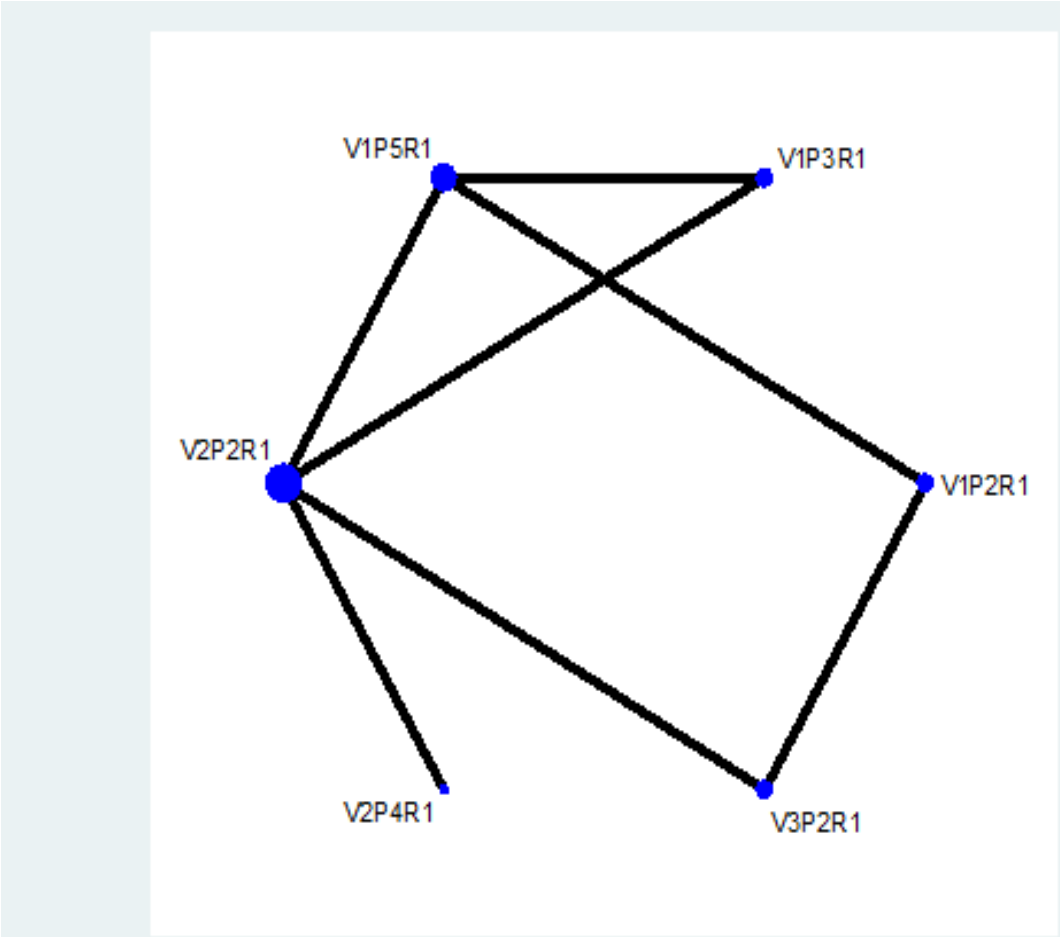


Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

6.3.5.2. Serious adverse events

Five trials (406 participants) provided data for the network meta-analysis on serious adverse events.[29, 255, 256, 258, 259] Two trials reported on total adverse events (of any severity), but did not clearly report on serious adverse events.[242, 257] There were 35 people with serious adverse events in the included studies (8.6%). The network plot is shown in Figure 6.8. The results and model fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model is provided in Table 6.22. The between-study standard deviation (tau) was 0.03. As indicated in Table 6.22, the fixed-effect model was preferred based on the DIC statistics. There was no evidence of inconsistency in the network. The pairwise ORs for the different treatment comparisons are shown in Table 6.23. As shown in Table 6.23, there was no evidence of any significant difference between the different treatments except for a significant increase in the proportion of people with serious adverse events in V1P5R1 (no vascular occlusion with radiofrequency dissecting sealer and no fibrin) compared with V1P2R1 (no vascular occlusion with clamp-crush and no fibrin) (OR 7.13; 95% CrI 1.77 to 28.65). The absolute proportion of people with serious adverse events based on an illustrative risk of 6.7% in the reference treatment is shown in the summary of findings for this outcome in Table 6.24. As shown in Figure 6.9, none of the treatment strategies ranked best with more than 90% probability. Also, none of the treatments ranked worst with more than 90% probability. As shown in Figure 6.10, there is more than 90% probability that V1P2R1 (no vascular occlusion with clamp-crush method and no fibrin) and V3P2R1 (intermittent vascular occlusion with clamp-crush and no fibrin) are within the three best treatments (of six treatments). This suggests that there is a high probability that these two treatment strategies are better than other treatment strategies with regards to serious adverse events. There is substantial uncertainty about the best or worst treatment strategy with regards to serious adverse events.

Figure 6.8: Network plot of the treatment strategies for the outcome serious adverse events.



Footnotes: circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Table 6.22: Results and model fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model for the outcome serious adverse events.

	Fixed-effect model	Random-effects model	Inconsistency model (random-effects)
d[2]	1 (95% CI -1.33 to 3.33)	0.77 (95% CI -6.22 to 7.76)	-
d[3]	1.96 (95% CI 0.57 to 3.36)	1.78 (95% CI -3.2 to 6.76)	-
d[4]	1.54 (95% CI -0.3 to 3.38)	1.22 (95% CI -4.57 to 7.01)	-
d[5]	1.54 (95% CI -2.49 to 5.58)	1.2 (95% CI -7.51 to 9.91)	-
d[6]	0.05 (95% CI -1.51 to 1.6)	0.1 (95% CI -4.91 to 5.11)	-
Dbar	44.12	41.43	41.4
pD	9.65	10.64	10.64
DIC	53.77	52.08	52.04

Footnotes: d[2] indicates the log odds ratio between treatment 2 and treatment 1, d[3] indicates the log odds ratio between treatment 3 and treatment 1, etc.; Dbar indicates the posterior mean of the residual deviance; pD indicates the effective number of parameters (leverage); DIC indicates the 'Deviance Information Criterion'. A lower Dbar indicates a better model fit. However, a model with lower DIC is generally chosen to aid better interpretation as it takes the model complexity into account. A lower DIC indicates a better model fit. Differences of less than 3 to 5 between the models are not considered important. Based on the information, fixed-effect model is the preferred model. There is no evidence of inconsistency since the difference in DIC between consistency and inconsistency models was not significant.

Table 6.23: Pairwise odds ratios of the different treatment comparisons for the outcome serious adverse events. Statistically significant results are in bold. There was no evidence of any significant difference between the different treatments except for a significant increase in the proportion of people with serious adverse events in V1P5R1 compared with V1P2R1.

	V1P3R1	**V1P5R1**	**V2P2R1**	**V2P4R1**	**V3P2R1**
V1P2R1	OR 2.72; 95% CI 0.27 to 27.92	**OR 7.13; 95% CI 1.77 to 28.65**	OR 4.68; 95% CI 0.74 to 29.47	OR 4.68; 95% CI 0.08 to 264.19	OR 1.05; 95% CI 0.22 to 4.96
V1P3R1	-	OR 2.62; 95% CI 0.17 to 39.46	OR 1.72; 95% CI 0.09 to 33.46	OR 1.72; 95% CI 0.02 to 181.18	OR 0.39; 95% CI 0.02 to 6.33
V1P5R1	-	-	OR 0.66; 95% CI 0.07 to 6.59	OR 0.66; 95% CI 0.01 to 46.8	OR 0.15; 95% CI 0.02 to 1.18
V2P2R1	-	-	-	OR 1; 95% CI 0.01 to 84.13	OR 0.22; 95% CI 0.02 to 2.49
V2P4R1	-	-	-	-	OR 0.22; 95% CI 0 to 16.89

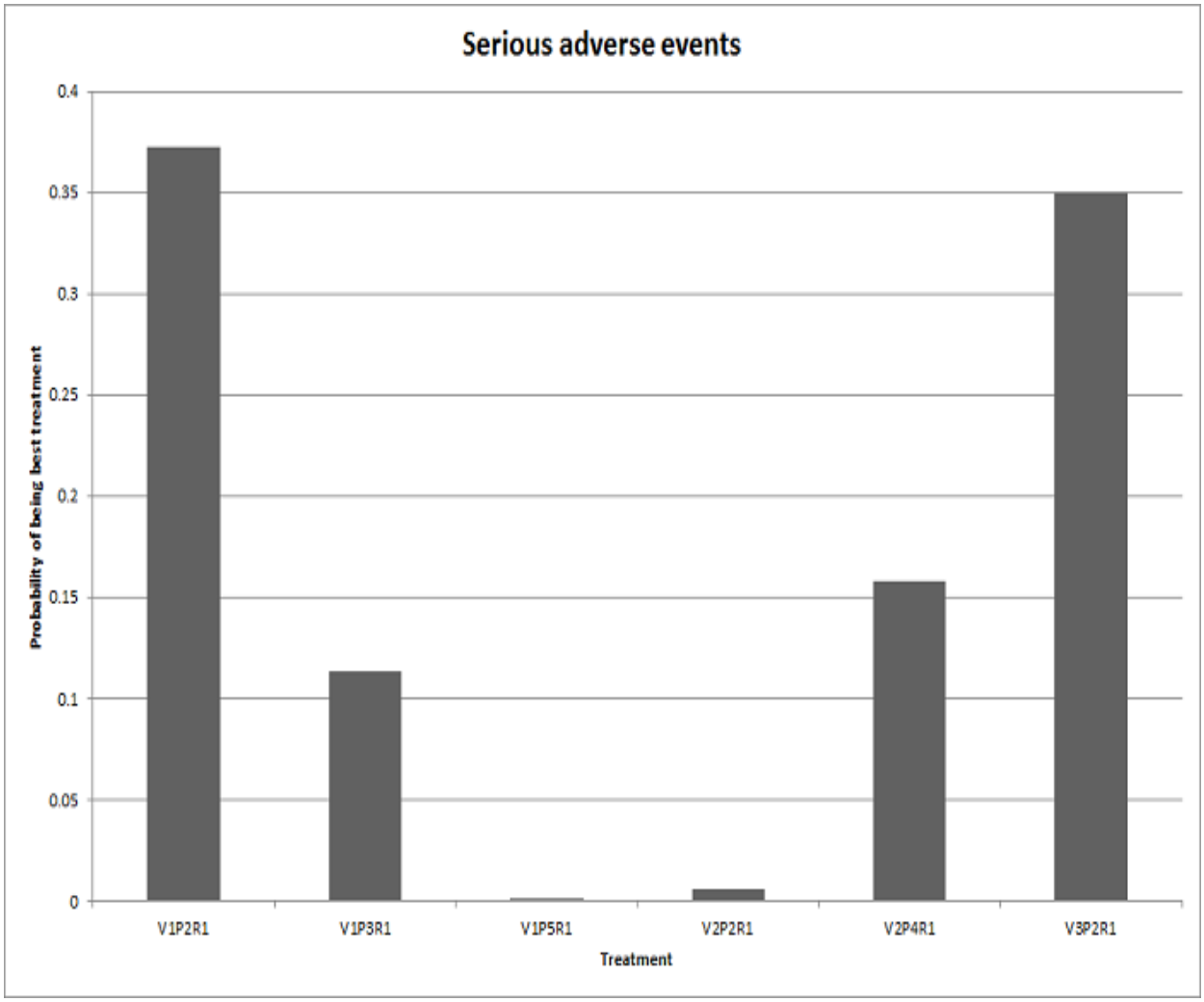
Footnotes: OR=odds ratio; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Table 6.24: Summary of findings for the outcome serious adverse events, including: quality of evidence, treatment strategies compared, the treatment effect for each treatment strategy from the network meta-analysis performed, and the corresponding illustrative risk for each treatment strategy.

Methods to decrease blood loss during liver resection (serious adverse events)		
Patient or population: people undergoing open liver resection **Settings:** secondary or tertiary **Intervention and control:** various treatments		
Number of trials (participants)	5 trials (406 participants)	
Overall quality of evidence	Very low i.e. we are very uncertain about the estimate	
Groups	**Illustrative risk**	**Treatment effect**
Assumed risk in control group (V1P2R1)*	67 per 1000	-
Corresponding risk in V1P3R1	163 per 1000 (19 to 667)	OR 2.72 (95% CI 0.27 to 27.92)
Corresponding risk in V1P5R1	339 per 1000 (113 to 673)	OR 7.13 (95% CI 1.77 to 28.65)
Corresponding risk in V2P2R1	252 per 1000 (50 to 679)	OR 4.68 (95% CI 0.74 to 29.47)
Corresponding risk in V2P4R1	252 per 1000 (6 to 950)	OR 4.68 (95% CI 0.08 to 264.19)
Corresponding risk in V3P2R1	70 per 1000 (16 to 263)	OR 1.05 (95% CI 0.22 to 4.96)
*The basis for the **assumed risk** was from the mean proportion with serious adverse events in control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).		

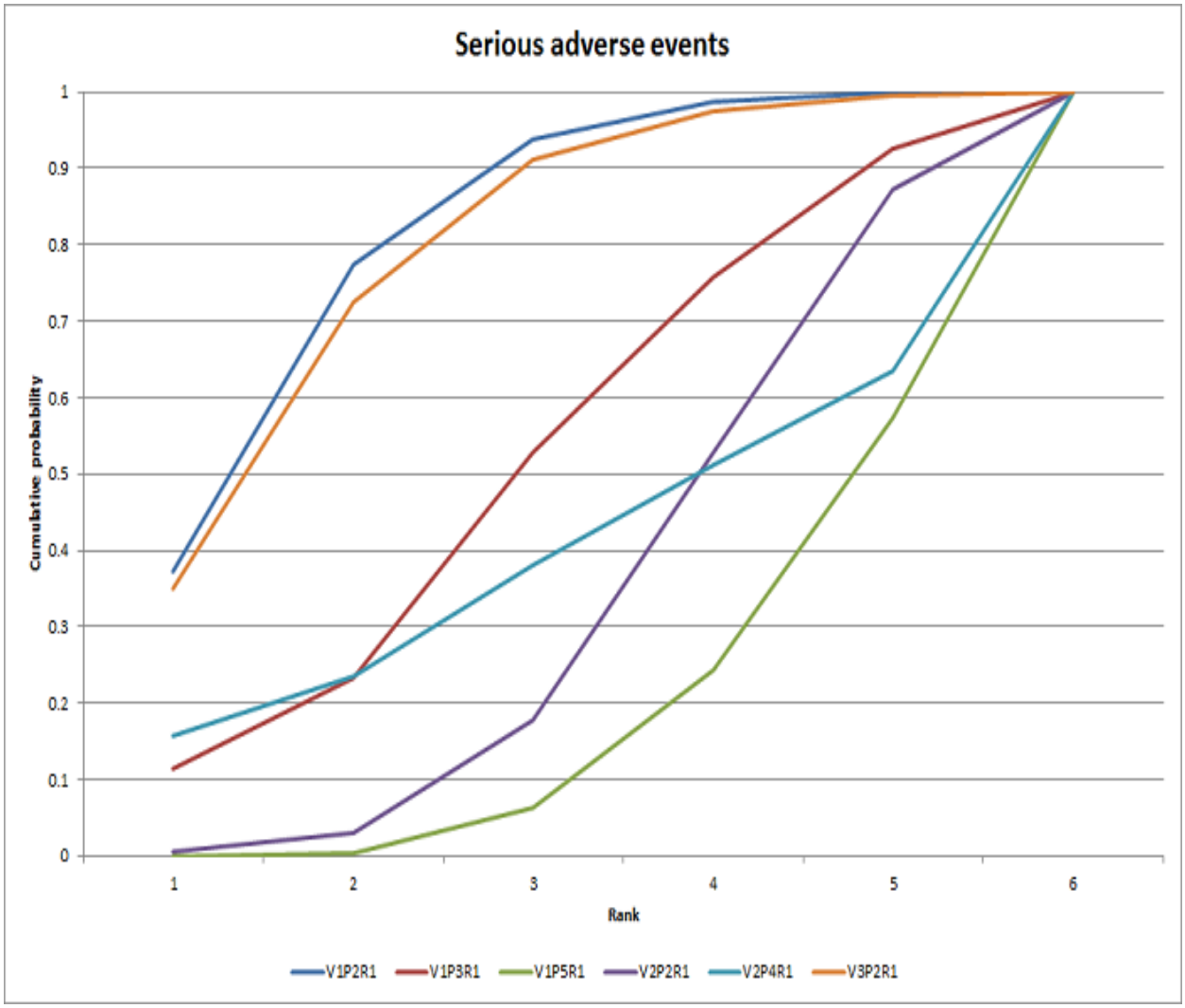
Footnotes: OR=odds ratio; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Figure 6.9: Probability of being best treatment strategy for the outcome serious adverse events. None of the treatment strategies ranked best with more than 90% probability, and there is a lot of uncertainty about the treatment strategy with the lowest mortality.



Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Figure 6.10: Cumulative probability of ranks of different treatment strategies for the outcome serious adverse events. There is more than 90% probability that V1P2R1 and V3P2R1 are within the three best treatments (of six treatments). This suggests that there is a high probability that these two treatment strategies are better than other treatment strategies with regards to serious adverse events. There is substantial uncertainty about the worst treatment strategy with regards to serious adverse events.

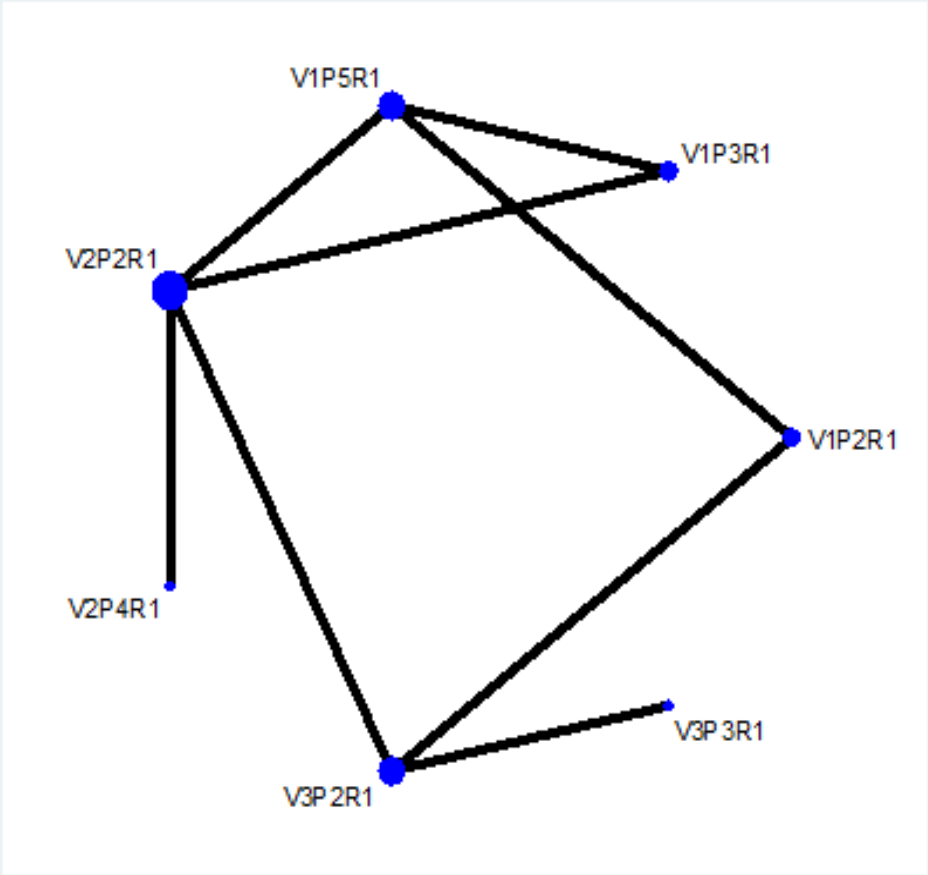


Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

6.3.5.3. Proportion of patients transfused

Six trials (446 participants) provided data for the network meta-analysis on proportion of patients needed to be transfused.[29, 242, 255, 256, 258, 259] One trial did not report on the number of patients requiring allogeneic blood transfusion.[257] The network plot is shown in Figure 6.11. The results and model-fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model is provided in Table 6.25. As indicated in Table 6.25, the random-effects model was preferred based on the DIC statistics. The between study standard deviation (tau) was 0.61. There was no evidence of inconsistency in the network. The pairwise ORs for the different treatment comparisons are shown in Table 6.26. As shown in Table 6.26, there is no evidence of any significant difference in the proportion of people transfused between the different treatments. The absolute proportion of people requiring blood transfusion based on an illustrative risk of 15.7% in the reference treatment is shown in the summary of findings for this outcome in Table 6.27. As shown in Figure 6.12, none of the treatments ranked best with more than 90% probability. Also, none of the treatments ranked worst with more than 90% probability. As shown in Figure 6.13, there is substantial uncertainty about the treatment strategy resulting in the lowest or the highest proportion of people needed to be transfused. For example, there was more than 90% probability that V2P2R1 (continuous vascular occlusion with clamp-crush and no fibrin) was within the five best treatments (of seven treatments) and that V1P2R1 (no vascular occlusion with clamp-crush and no fibrin) was within the six best treatments (of seven treatments).

Figure 6.11: Network plot of the treatment strategies for the outcome proportion of patients transfused.



Footnotes: circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Table 6.25: Results and model fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model for the outcome proportion of patients transfused.

	Fixed-effect model	Random-effects model	Inconsistency model (random-effects)
d[2]	1.29 (95% CI -0.32 to 2.9)	1.8 (95% CI -5.75 to 9.35)	-
d[3]	-0.03 (95% CI -1.08 to 1.01)	0.49 (95% CI -4.94 to 5.92)	-
d[4]	-0.04 (95% CI -1.43 to 1.36)	-0.24 (95% CI -6.63 to 6.15)	-
d[5]	-0.26 (95% CI -1.93 to 1.41)	-0.46 (95% CI -9.32 to 8.41)	-
d[6]	0.8 (95% CI -0.46 to 2.07)	1.22 (95% CI -4.4 to 6.85)	-
d[7]	1.36 (95% CI -1.1 to 3.82)	1.8 (95% CI -6.77 to 10.36)	-
Dbar	63.46	56.44	56.61
pD	12.02	13.01	12.89
DIC	75.48	69.45	69.51

Footnotes: d[2] indicates the log odds ratio between treatment 2 and treatment 1, d[3] indicates the log odds ratio between treatment 3 and treatment 1, etc.; Dbar indicates the posterior mean of the residual deviance; pD indicates the effective number of parameters (leverage); DIC indicates the 'Deviance Information Criterion'. A lower Dbar indicates a better model fit. However, a model with lower DIC is generally chosen to aid better interpretation as it takes the model complexity into account. A lower DIC indicates a better model fit. Differences of less than 3 to 5 between the models are not considered important. Based on the information, random-effects model is the preferred model. There is no evidence of inconsistency since the difference in DIC between consistency and inconsistency models was not significant.

Table 6.26: Pairwise odds ratios of the different treatment comparisons for the outcome proportion of patients transfused. There is no evidence of any significant difference in the proportion of people transfused between the different treatment strategies.

	V1P3R1	**V1P5R1**	**V2P2R1**	**V2P4R1**	**V3P2R1**	**V3P3R1**
V1P2R1	OR 6.06; 95% CI 0 to 11486.87	OR 1.64; 95% CI 0.01 to 373.55	OR 0.79; 95% CI 0 to 469.31	OR 0.63; 95% CI 0 to 4494.19	OR 3.4; 95% CI 0.01 to 941.28	OR 6.03; 95% CI 0 to 31671.1
V1P3R1	-	OR 0.27; 95% CI 0 to 2950.65	OR 0.13; 95% CI 0 to 2563.91	OR 0.1; 95% CI 0 to 11933.13	OR 0.56; 95% CI 0 to 6873.03	OR 1; 95% CI 0 to 90479.42
V1P5R1	-	-	OR 0.48; 95% CI 0 to 2111.73	OR 0.39; 95% CI 0 to 12705.22	OR 2.08; 95% CI 0 to 5166.35	OR 3.68; 95% CI 0 to 93690.74
V2P2R1	-	-	-	OR 0.81; 95% CI 0 to 44995.95	OR 4.32; 95% CI 0 to 21534.25	OR 7.66; 95% CI 0 to 336044.28
V2P4R1	-	-	-	-	OR 5.37; 95% CI 0 to 194906	OR 9.51; 95% CI 0 to 2152551.81
V3P2R1	-	-	-	-	-	OR 1.77; 95% CI 0 to 50000.24

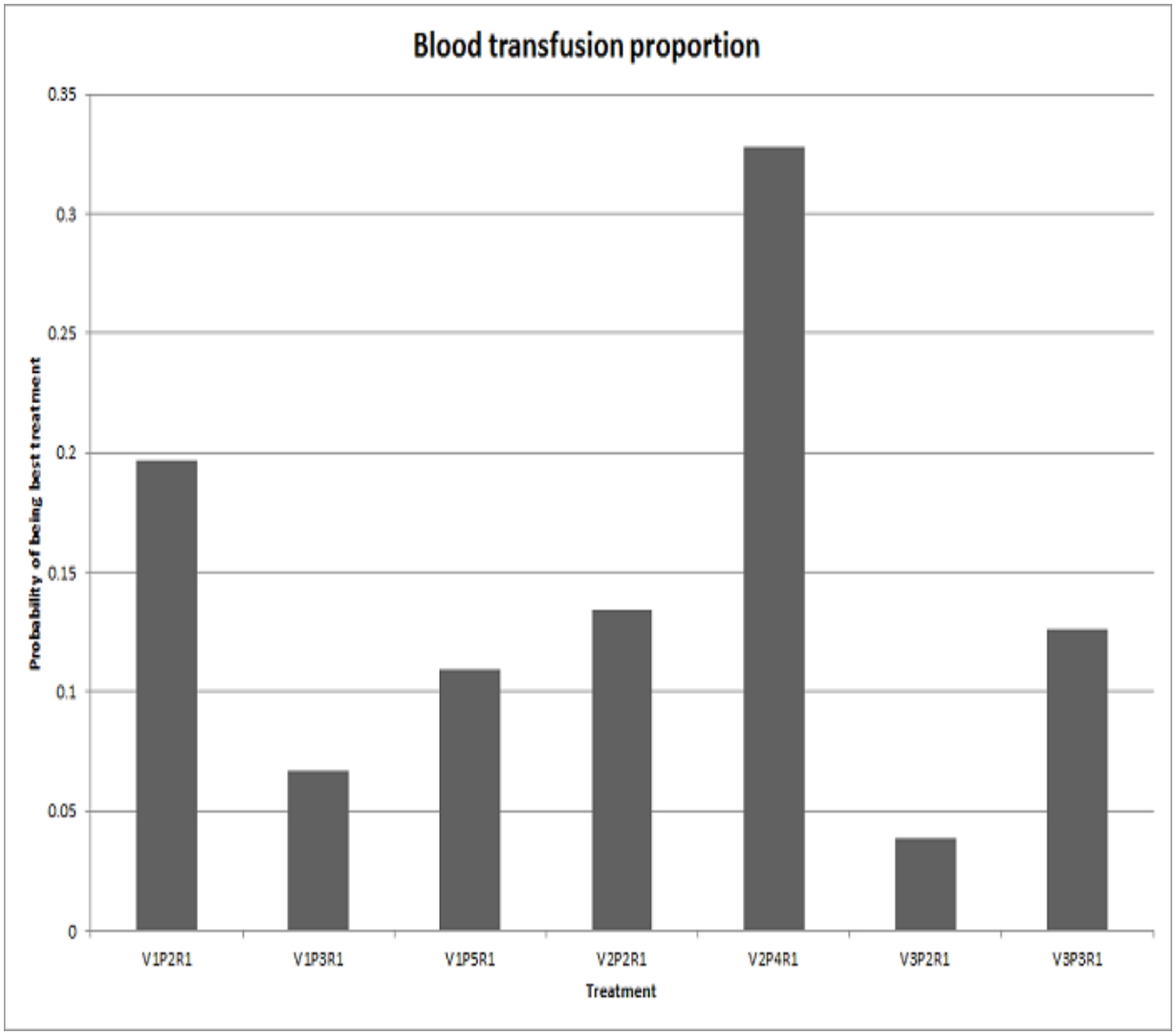
Footnotes: OR=odds ratio; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Table 6.27: Summary of findings for the outcome proportion of patients transfused, including: quality of evidence, treatment strategies compared, the treatment effect for each treatment strategy from the network meta-analysis performed, and the corresponding illustrative risk for each treatment strategy.

Methods to decrease blood loss during liver resection (Blood transfusion proportion)		
Patient or population: people undergoing open liver resection **Settings:** secondary or tertiary **Intervention and control:** various treatments		
Number of trials (participants)	6 trials (446 participants)	
Overall quality of evidence	Very low i.e. we are very uncertain about the estimate	
Groups	**Illustrative risk**	**Treatment effect**
Assumed risk in control group (V1P2R1)	157 per 1000	-
Corresponding risk in V1P3R1	530 per 1000 (0 to 1000)	OR 6.06; 95% CI 0 to 11486.87
Corresponding risk in V1P5R1	234 per 1000 (2 to 986)	OR 1.64; 95% CI 0.01 to 373.55
Corresponding risk in V2P2R1	128 per 1000 (0 to 989)	OR 0.79; 95% CI 0 to 469.31
Corresponding risk in V2P4R1	105 per 1000 (0 to 999)	OR 0.63; 95% CI 0 to 4494.19
Corresponding risk in V3P2R1	388 per 1000 (2 to 994)	OR 3.4; 95% CI 0.01 to 941.28
Corresponding risk in V3P3R1	529 per 1000 (0 to 1000)	OR 6.03; 95% CI 0 to 31671.1
*The basis for the **assumed risk** was from the mean proportion with blood transfusion in control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).		

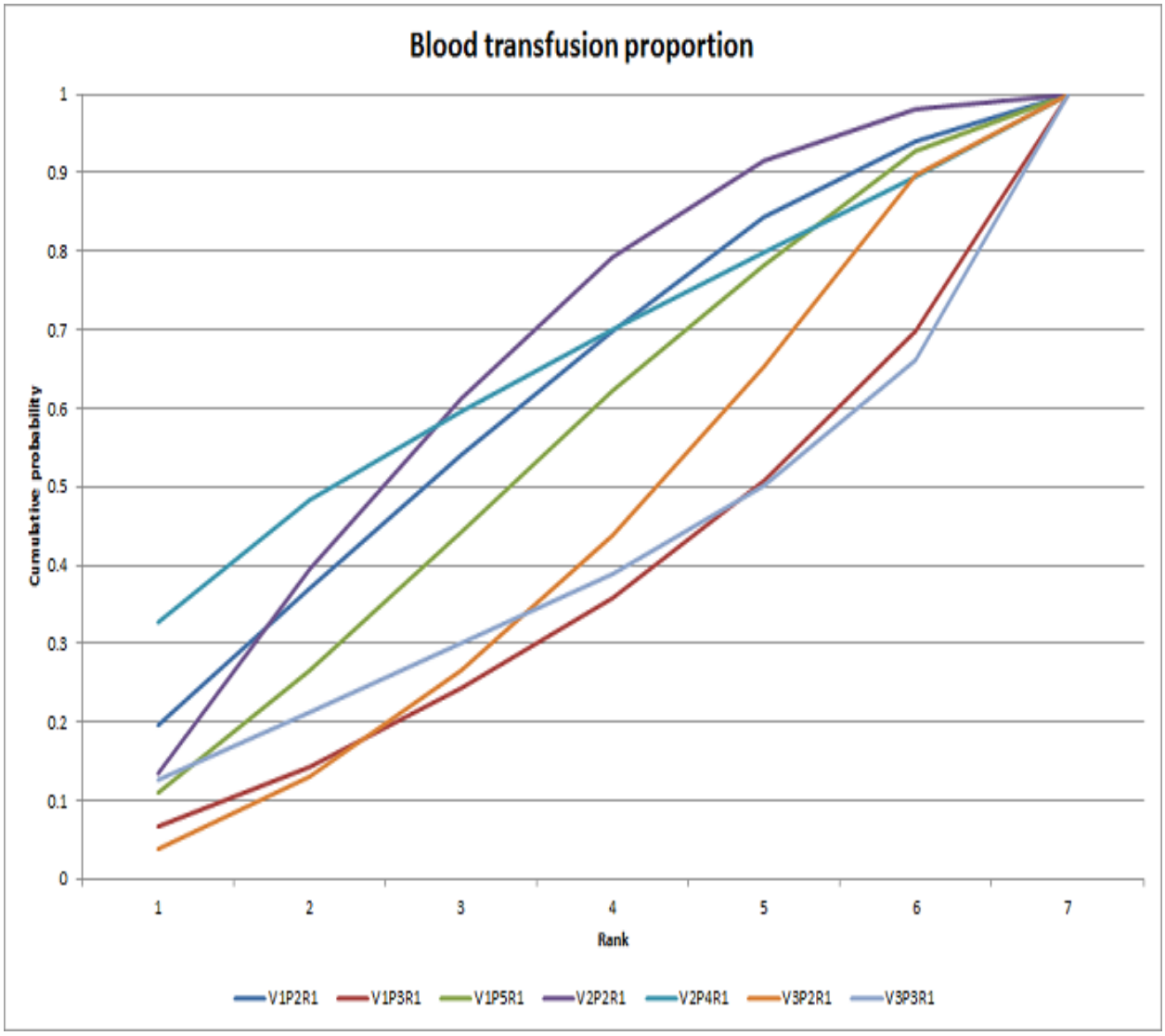
Footnotes: OR=odds ratio; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.12: Probability of being best treatment strategy for the outcome proportion of patients transfused. None of the treatment strategies ranked best with more than 90% probability, and there is a lot of uncertainty about the treatment strategy with the lowest proportion of patients transfused.



Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.13: Cumulative probability of ranks of different treatment strategies for the outcome proportion of patients transfused. There was more than 90% probability that V2P2R1 was within the five best treatments (of seven treatments) and that V1P2R1 was within the six best treatments (of seven treatments). There is substantial uncertainty about the treatment strategy resulting in the lowest or the highest proportion of people needed to be transfused.

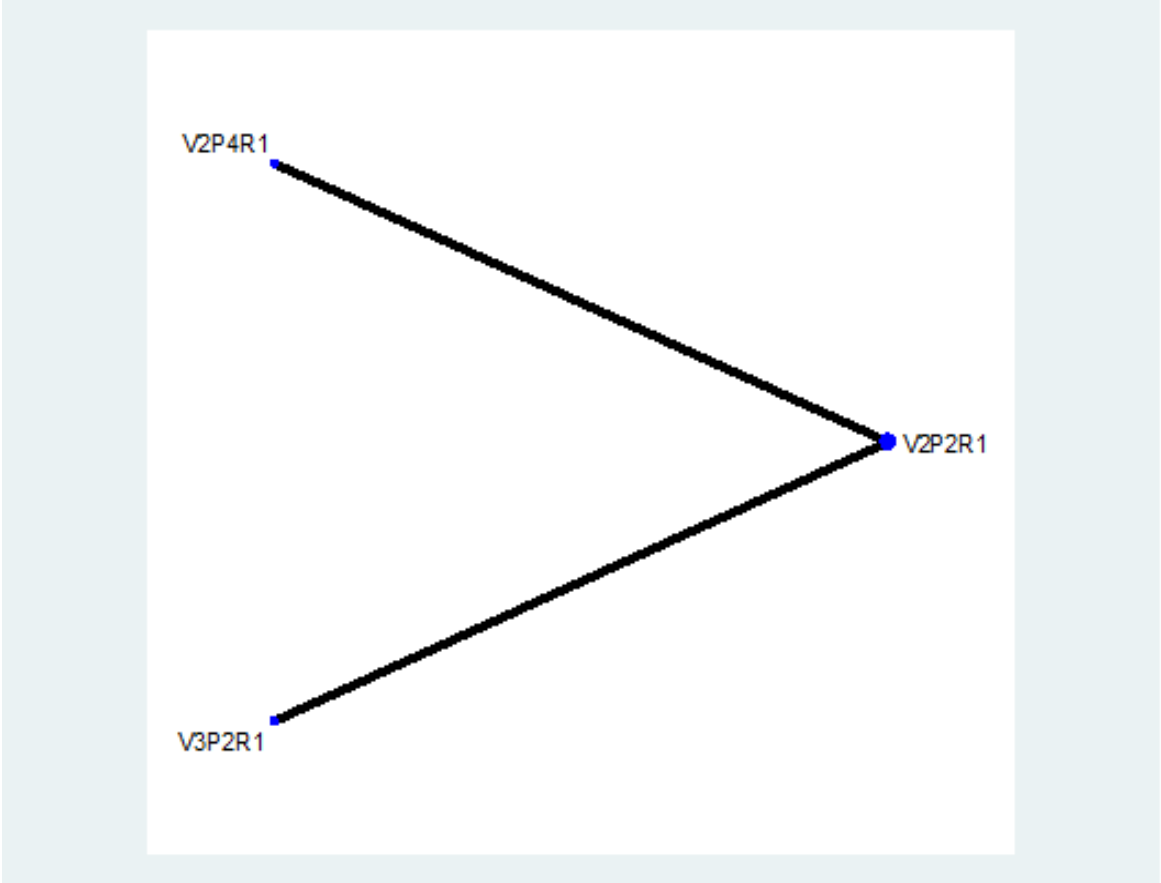


Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

6.3.5.4. Quantity of blood transfused

Two trials (155 participants) provided data for the network meta-analysis on quantity of blood transfused.[258, 259] The other five trials [29, 242, 255-257] did not report on the quantity of perioperative blood transfusion required. The network plot for this outcome is shown in Figure 6.14, and it demonstrates only the three treatment strategies included in the two trials[258, 259] providing data on the quantity of perioperative blood transfusion. The results and model-fit of the fixed-effect model and random-effects model is provided in Table 6.28. The between-study standard deviation (tau) was 0. As indicated in Table 6.28, the fixed-effect model was preferred based on the DIC statistics. The model-fit of the inconsistency model was not reported because there was no closed loop in the network. The pairwise MDs for the different treatment comparisons are shown in Table 6.29. As shown in Table 6.29, people undergoing liver resection by V3P2R1 (intermittent vascular occlusion with clamp-crush and no fibrin) had significantly higher amounts of blood transfused than people undergoing liver resection by V2P2R1 (continuous vascular occlusion with clamp-crush and no fibrin) (MD 1.2 units; 95% CrI 0.08 to 2.32). There were no significant differences in the other comparisons. As shown in Figure 6.15, none of the treatment strategies ranked best with more than 90% probability. As shown in Figure 6.16, there was more than 90% probability that V2P2R1 (continuous vascular occlusion with clamp-crush and no fibrin) and V2P4R1 (continuous vascular occlusion with sharp dissection and no fibrin) are within the two best treatments. This suggests that these two treatment strategies are better than V3P2R1 (intermittent vascular occlusion with clamp-crush and no fibrin) with regards to the quantity of blood transfused. There was a 90.2% probability that V3P2R1 (intermittent vascular occlusion with clamp-crush and no fibrin) was the worst treatment strategy with regards to the quantity of blood transfused, out of the three treatment strategies compared for this outcome.

Figure 6.14: Network plot of the treatment strategies for the outcome quantity of blood transfused. It demonstrates only the three treatment strategies included in the two trials[258, 259] providing data on the quantity of perioperative blood transfusion.



Footnotes: circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Table 6.28: Results and model fit of the fixed-effect model and random-effects model for the outcome quantity of blood transfused. The model-fit of the inconsistency model was not reported because there was no closed loop in the network.

	Fixed-effect model	Random-effects model
d[2]	0 (95% CI -1.36 to 1.36)	0 (95% CI -5.83 to 5.83)
d[3]	1.2 (95% CI 0.08 to 2.32)	1.2 (95% CI -4.57 to 6.96)
Dbar	4.66	4.67
pD	4	4
DIC	8.65	8.67

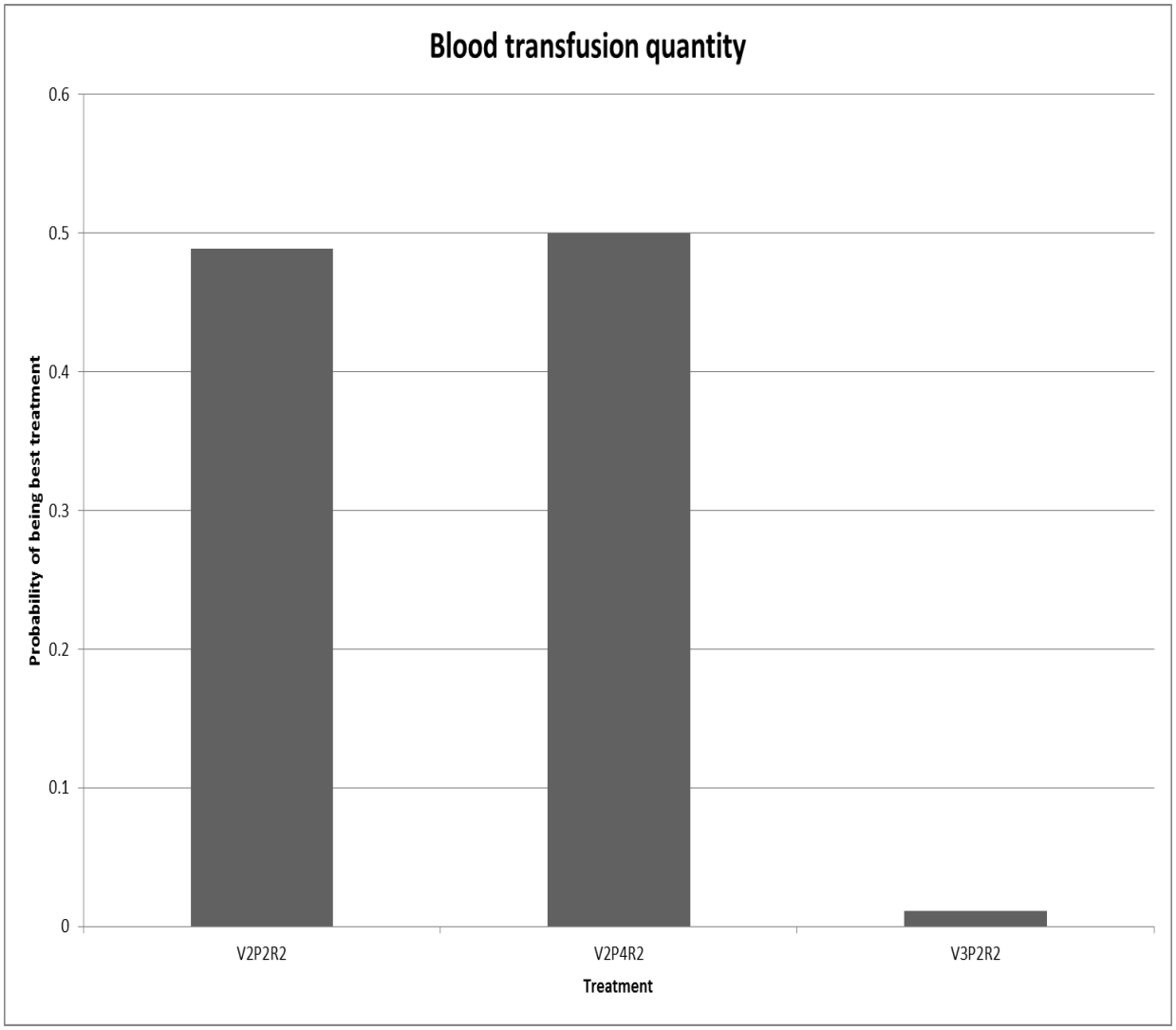
Footnotes: d[2] indicates the log odds ratio between treatment 2 and treatment 1, d[3] indicates the log odds ratio between treatment 3 and treatment 1; Dbar indicates the posterior mean of the residual deviance; pD indicates the effective number of parameters (leverage); DIC indicates the 'Deviance Information Criterion'. A lower Dbar indicates a better model fit. However, a model with lower DIC is generally chosen to aid better interpretation as it takes the model complexity into account. A lower DIC indicates a better model fit. Differences of less than 3 to 5 between the models are not considered important. Based on the information, fixed-effect model is the preferred model.

Table 6.29: Pairwise mean differences of the different treatment comparisons for the outcome quantity of blood transfused. Statistically significant results are in bold. People undergoing liver resection by V3P2R1 had significantly higher amounts of blood transfused than people undergoing liver resection by V2P2R1.

	V2P4R1	V3P2R1
V2P2R1	MD 0; 95% CI -1.36 to 1.36	**MD 1.2; 95% CI 0.08 to 2.32**
V2P4R1	-	MD 1.2; 95% CI -0.56 to 2.96

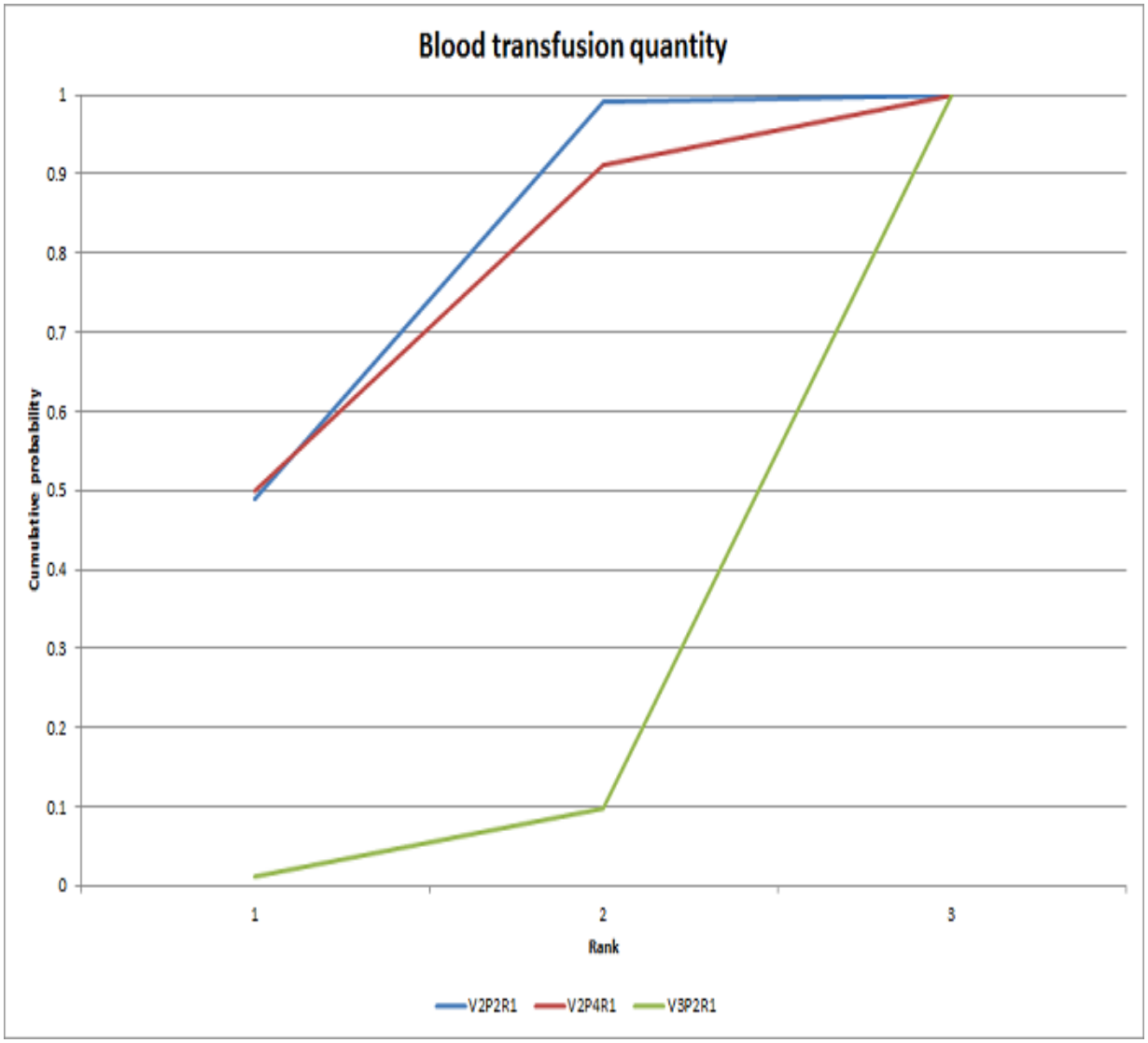
Footnotes: MD=mean difference; 95% CI=95% confidence intervals; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Figure 6.15: Probability of being best treatment strategy for the outcome quantity of blood transfused. None of the treatment strategies ranked best with more than 90% probability.



Footnotes: V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Figure 6.16: Cumulative probability of ranks of different treatments for the outcome quantity of blood transfused. There was more than 90% probability that V2P2R1 and V2P4R1 are within the two best treatments. There was a 90.2% probability that V3P2R1 was the worst treatment strategy with regards to the quantity of blood transfused, out of the three treatment strategies compared for this outcome.

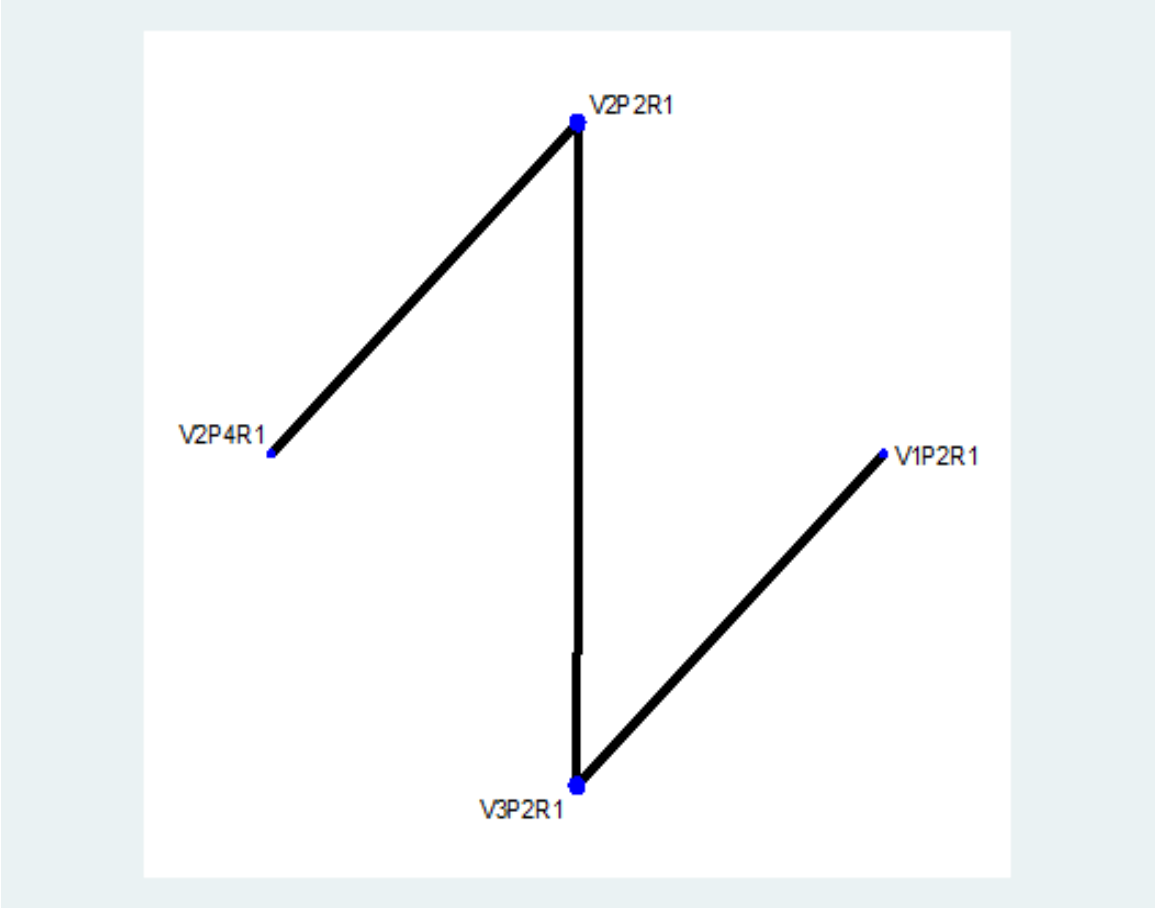


Footnotes: V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

6.3.5.5. Operative blood loss

Four trials reported on operative blood loss during hepatectomy.[29, 257-259] The other three trials did not report on operative blood loss.[242, 255, 256] One trial[257] reporting on operative blood loss had to be excluded from the analysis of this outcome because the treatment strategies it reported on were not directly compared with the treatment strategies of the other trials reporting on this outcome (i.e. not connected to the network plot for this outcome). Therefore, three trials (281 participants) provided data for the network meta-analysis on operative blood loss. [29, 258, 259] The network plot for this outcome is shown in Figure 6.17. The results and model-fit of the fixed-effect model and random-effects model is provided in Table 6.30. The between-study standard deviation (tau) was 0.02. As indicated in Table 6.30, the fixed effect model was preferred based on the DIC statistics. The model-fit of the inconsistency model was not reported because there was no closed loop in the network. The pairwise MDs for the different treatment comparisons are shown in Table 6.31. As shown in Table 6.31, people undergoing liver resection by V2P2R1 (continuous vascular occlusion with clamp crush and no fibrin) had significantly lower blood loss than those undergoing liver resection by V1P2R1 (no vascular occlusion with clamp-crush and no fibrin) (MD -130.9 mL; 95% CrI -255.89 to -5.91). There were no significant differences in the other comparisons. As shown in Figure 6.18 and Figure 6.19, V2P2R1 (continuous vascular occlusion with clamp-crush and no fibrin) was ranked the best treatment strategy with regards to operative blood loss with more than 90% probability (96.0% probability). There is substantial uncertainty about the worst treatment strategy with regards to operative blood loss.

Figure 6.17: Network plot of the treatment strategies for the outcome operative blood loss.



Footnotes: circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Table 6.30: Results and model fit of the fixed-effect model and random-effects model for the outcome operative blood loss. The model-fit of the inconsistency model was not reported because there was no closed loop in the network.

	Fixed-effect model	Random-effects model
d[2]	-130.9 (95% CI -255.89 to -5.91)	-127.9 (95% CI -255.59 to -0.21)
d[3]	39.59 (95% CI -111.37 to 190.55)	37.61 (95% CI -113.21 to 188.43)
d[4]	3.62 (95% CI -64.31 to 71.56)	3.45 (95% CI -64.7 to 71.6)
Dbar	70.77	70.65
pD	4.24	4.24
DIC	75.01	74.89

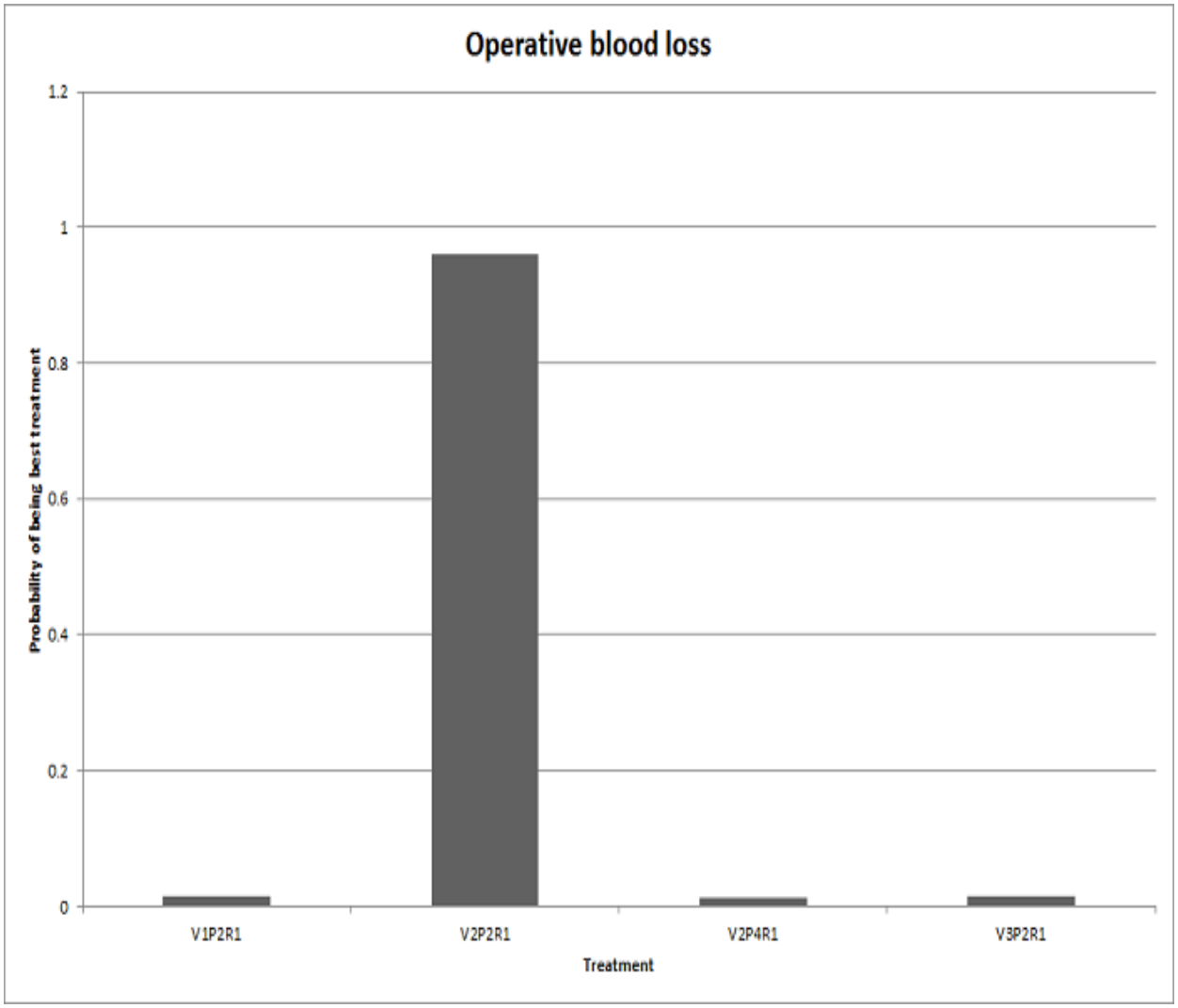
Footnotes: d[2] indicates the log odds ratio between treatment 2 and treatment 1, d[3] indicates the log odds ratio between treatment 3 and treatment 1, etc.; Dbar indicates the posterior mean of the residual deviance; pD indicates the effective number of parameters (leverage); DIC indicates the 'Deviance Information Criterion'. A lower Dbar indicates a better model fit. However, a model with lower DIC is generally chosen to aid better interpretation as it takes the model complexity into account. A lower DIC indicates a better model fit. Differences of less than 3 to 5 between the models are not considered important. Based on the information, fixed-effect model is the preferred model.

Table 6.31: Pairwise mean differences of the different treatment comparisons for the outcome operative blood loss. Statistically significant results are in bold. People undergoing liver resection by V2P2R1 had significantly lower blood loss than those undergoing liver resection by V1P2R1. There were no significant differences in the other comparisons.

	V2P2R1	V2P4R1	V3P2R1
V1P2R1	**MD -130.9; 95% CI -255.89 to -5.91**	MD 39.59; 95% CI -111.37 to 190.55	MD 3.62; 95% CI -64.31 to 71.56
V2P2R1	-	MD 170.49; 95% CI -25.5 to 366.48	MD 134.52; 95% CI -7.73 to 276.78
V2P4R1	-	-	MD -35.97; 95% CI -201.51 to 129.57

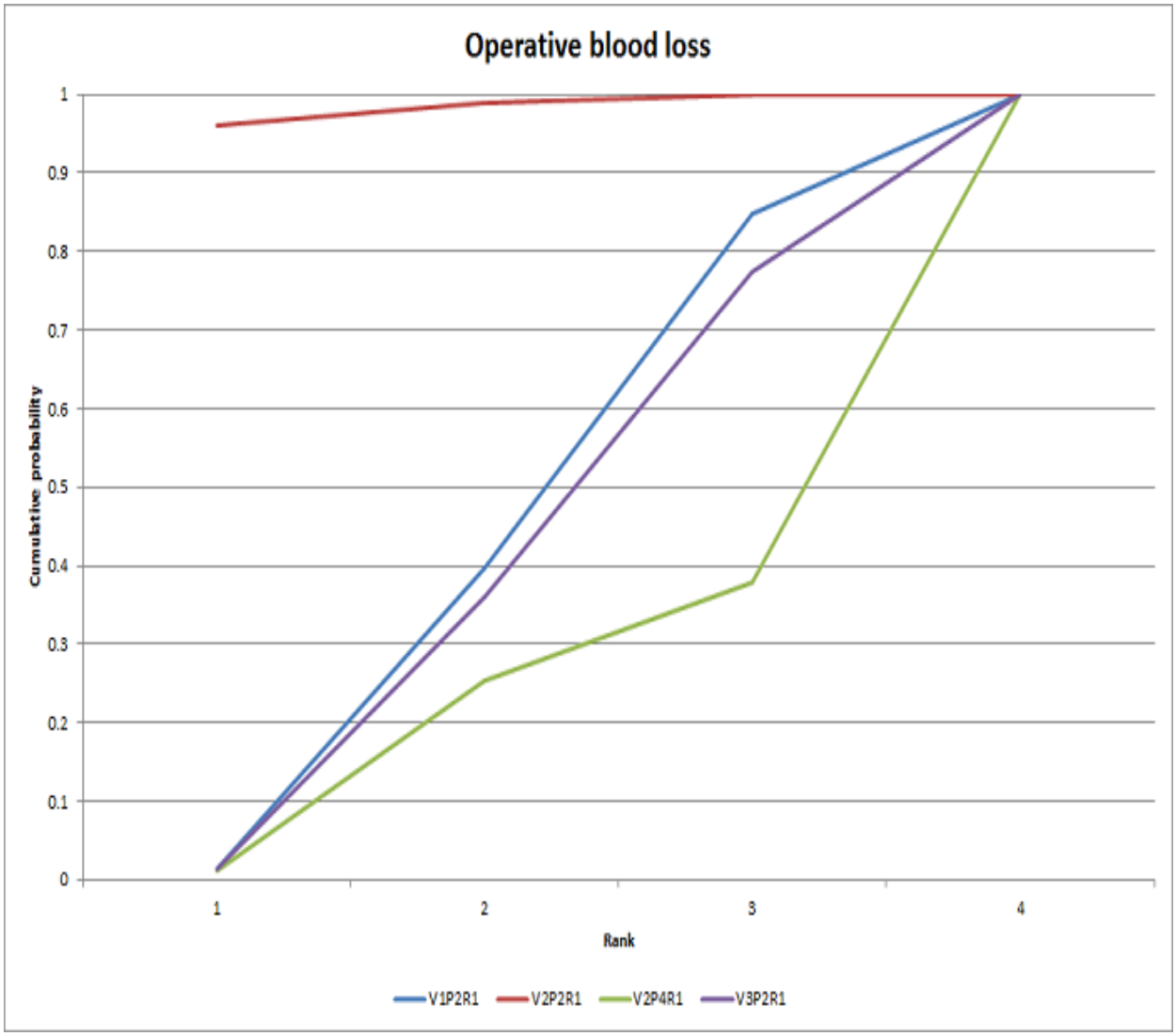
Footnotes: MD=mean difference; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Figure 6.18: Probability of being best treatment strategy for the outcome operative blood loss. V2P2R1 was ranked the best treatment strategy with regards to operative blood loss with 96.0% probability.



Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

Figure 6.19: Cumulative probability of ranks of different treatments for the outcome operative blood loss. V2P2R1 ranked the best treatment strategy with regards to operative blood loss with more than 90% probability. There is substantial uncertainty about the worst treatment strategy with regards to operative blood loss.

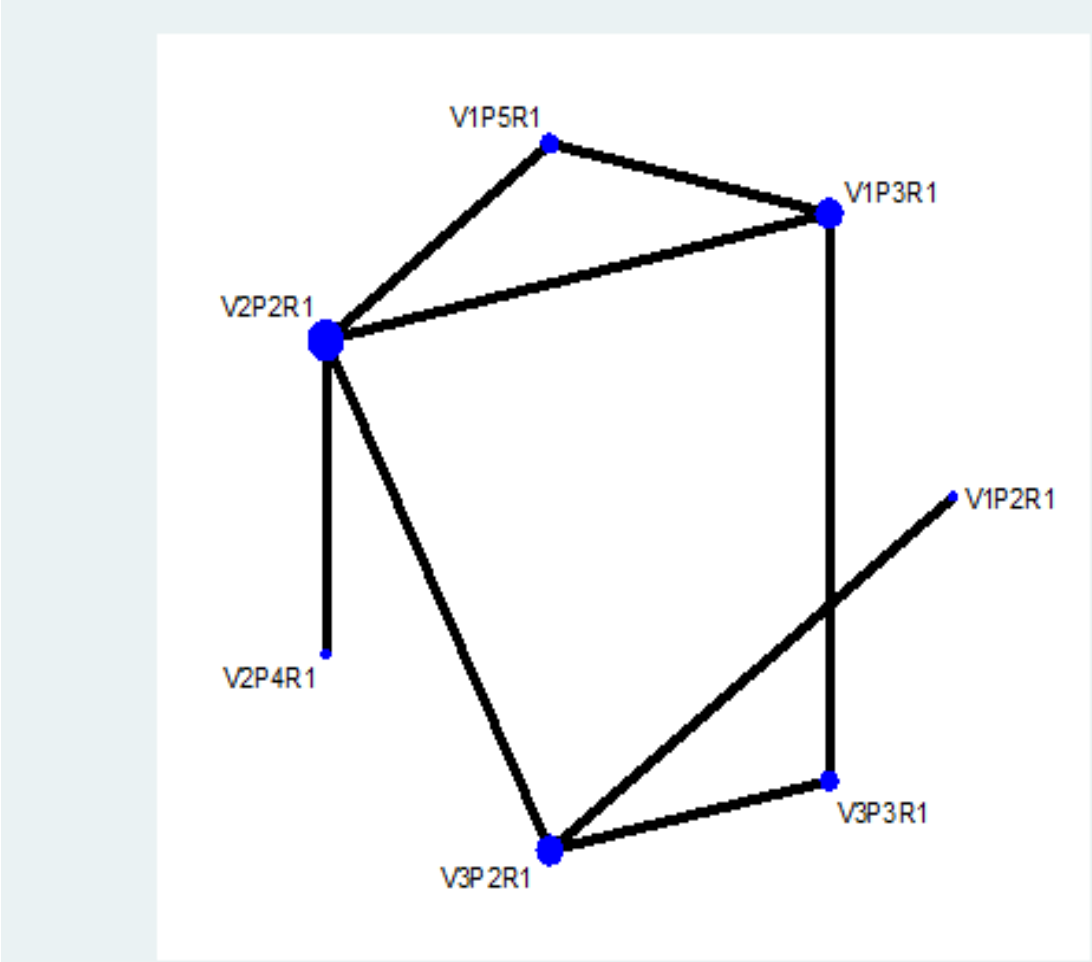


Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin.

6.3.5.6. Length of hospital stay

Six trials (446 participants) provided data for the network meta-analysis on length of hospital stay.[29, 242, 255, 257-259] One trial did not report the postoperative length of hospital stay.[256] The network plot is shown in Figure 6.20. The results and model-fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model is provided in Table 6.32. The between study standard deviation (tau) was 0.01. As indicated in Table 6.32, the fixed-effect model was preferred based on the DIC statistics. There was no evidence of inconsistency in the network. The pairwise MDs for the different treatment comparisons are shown in Table 6.33. As shown in Table 6.33, there was no evidence of any significant difference in the length of hospital stay between the different treatments. As shown in Figure 6.21, none of the treatment strategies ranked best with more than 90% probability. Also, none of the treatment strategies ranked worst with more than 90% probability. As shown in Figure 6.22, there is more than 90% probability that V3P3R1 (intermittent vascular occlusion with CUSA and no fibrin) is within the three best treatments (of seven treatments). There is more than 90% probability that V1P2R1 (no vascular occlusion with clamp-crush and no fibrin) and V3P2R1 (intermittent vascular occlusion with clamp-crush and no fibrin) are within the five best treatments. There is substantial uncertainty about the treatment strategy with the lowest or highest length of hospital stay.

Figure 6.20: Network plot of the treatment strategies for the outcome length of hospital stay.



Footnotes: circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Table 6.32: Results and model fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model for the outcome length of hospital stay.

	Fixed-effect model	Random-effects model	Inconsistency model (random-effects)
d[2]	2.29 (95% CI -2.03 to 6.61)	2.28 (95% CI -5.82 to 10.39)	-
d[3]	2.29 (95% CI -3.01 to 7.58)	2.29 (95% CI -6.94 to 11.51)	-
d[4]	2.29 (95% CI -1.57 to 6.15)	2.29 (95% CI -5.18 to 9.75)	-
d[5]	3.28 (95% CI -2.59 to 9.15)	3.29 (95% CI -6.64 to 13.22)	-
d[6]	0.3 (95% CI -1.11 to 1.71)	0.29 (95% CI -4.77 to 5.35)	-
d[7]	-1.21 (95% CI -5.19 to 2.78)	-1.21 (95% CI -8.77 to 6.34)	-
Dbar	41.68	42.11	42.7
pD	11.99	12.41	13.01
DIC	53.67	54.52	55.7

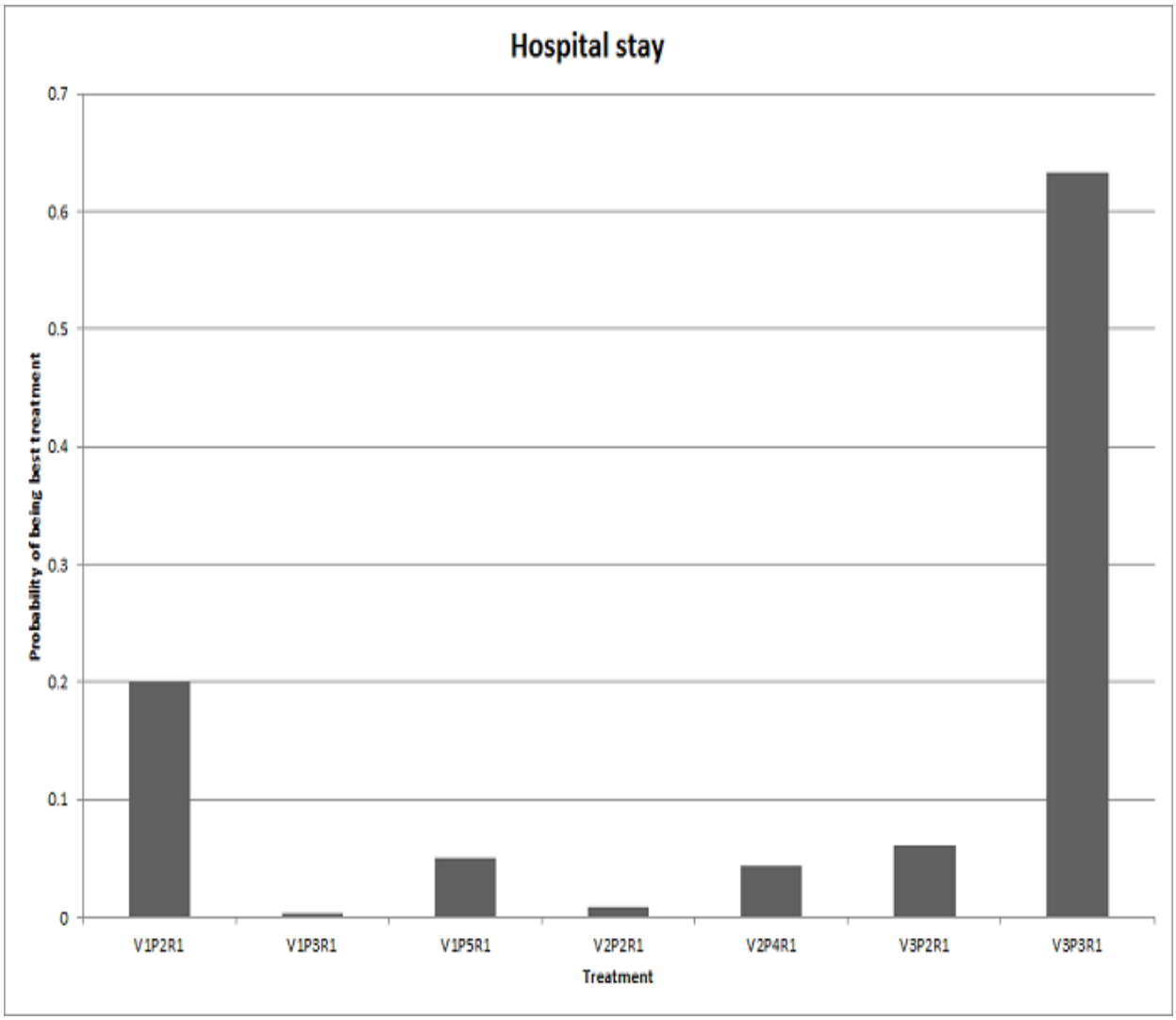
Footnotes: d[2] indicates the log odds ratio between treatment 2 and treatment 1, d[3] indicates the log odds ratio between treatment 3 and treatment 1, etc.; Dbar indicates the posterior mean of the residual deviance; pD indicates the effective number of parameters (leverage); DIC indicates the 'Deviance Information Criterion'. A lower Dbar indicates a better model fit. However, a model with lower DIC is generally chosen to aid better interpretation as it takes the model complexity into account. A lower DIC indicates a better model fit. Differences of less than 3 to 5 between the models are not considered important. Based on the information, fixed-effect model is the preferred model. There is no evidence of inconsistency since the difference in DIC between consistency and inconsistency models was not significant.

Table 6.33: Pairwise mean differences of the different treatment comparisons for the outcome length of hospital stay. There was no evidence of any significant difference in the length of hospital stay between the different treatment strategies.

	V1P3R1	**V1P5R1**	**V2P2R1**	**V2P4R1**	**V3P2R1**	**V3P3R1**
V1P2R1	MD 2.29; 95% CI -2.03 to 6.61	MD 2.29; 95% CI -3.01 to 7.58	MD 2.29; 95% CI -1.57 to 6.15	MD 3.28; 95% CI -2.59 to 9.15	MD 0.3; 95% CI -1.11 to 1.71	MD -1.21; 95% CI -5.19 to 2.78
V1P3R1	-	MD 0; 95% CI -6.84 to 6.83	MD 0; 95% CI -5.79 to 5.79	MD 0.99; 95% CI -6.3 to 8.28	MD -1.99; 95% CI -6.54 to 2.55	MD -3.5; 95% CI -9.37 to 2.38
V1P5R1	-	-	MD 0; 95% CI -6.55 to 6.55	MD 0.99; 95% CI -6.91 to 8.9	MD -1.99; 95% CI -7.47 to 3.49	MD -3.5; 95% CI -10.12 to 3.13
V2P2R1	-	-	-	MD 0.99; 95% CI -6.03 to 8.02	MD -1.99; 95% CI -6.1 to 2.12	MD -3.5; 95% CI -9.04 to 2.05
V2P4R1	-	-	-	-	MD -2.98; 95% CI -9.02 to 3.06	MD -4.49; 95% CI -11.58 to 2.61
V3P2R1	-	-	-	-	-	MD -1.51; 95% CI -5.73 to 2.72

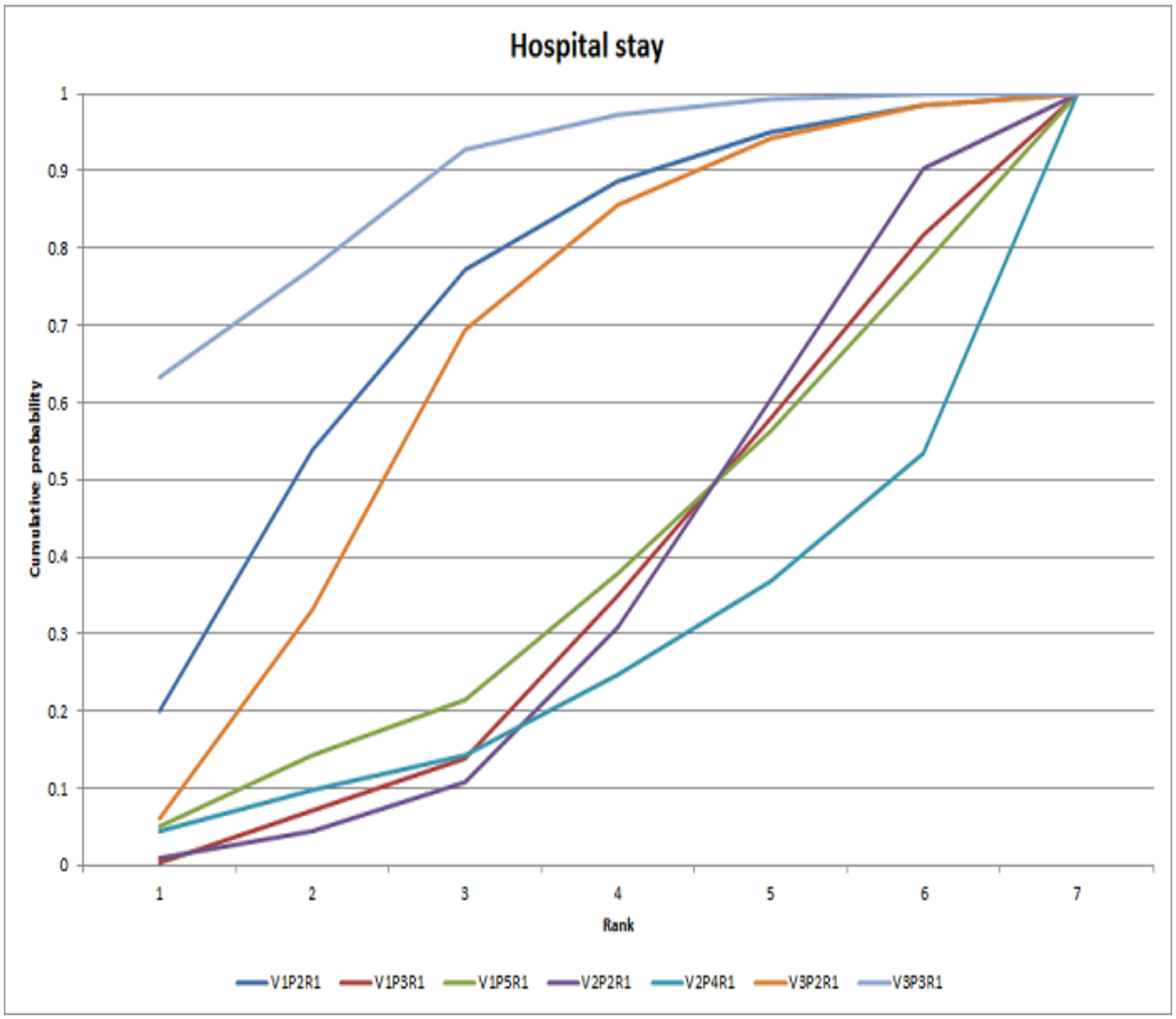
Footnotes: MD=mean difference; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.21: Probability of being best treatment for the outcome length of hospital stay. None of the treatment strategies ranked best with more than 90% probability.



Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.22: Cumulative probability of ranks of different treatment strategies for the outcome length of hospital stay. These is more than 90% probability that V3P3R1 is within the three best treatments (of seven treatments). These is more than 90% probability V1P2R1 and V3P2R1 are within the five best treatments. There is substantial uncertainty about the treatment strategy with the lowest or highest length of hospital stay.

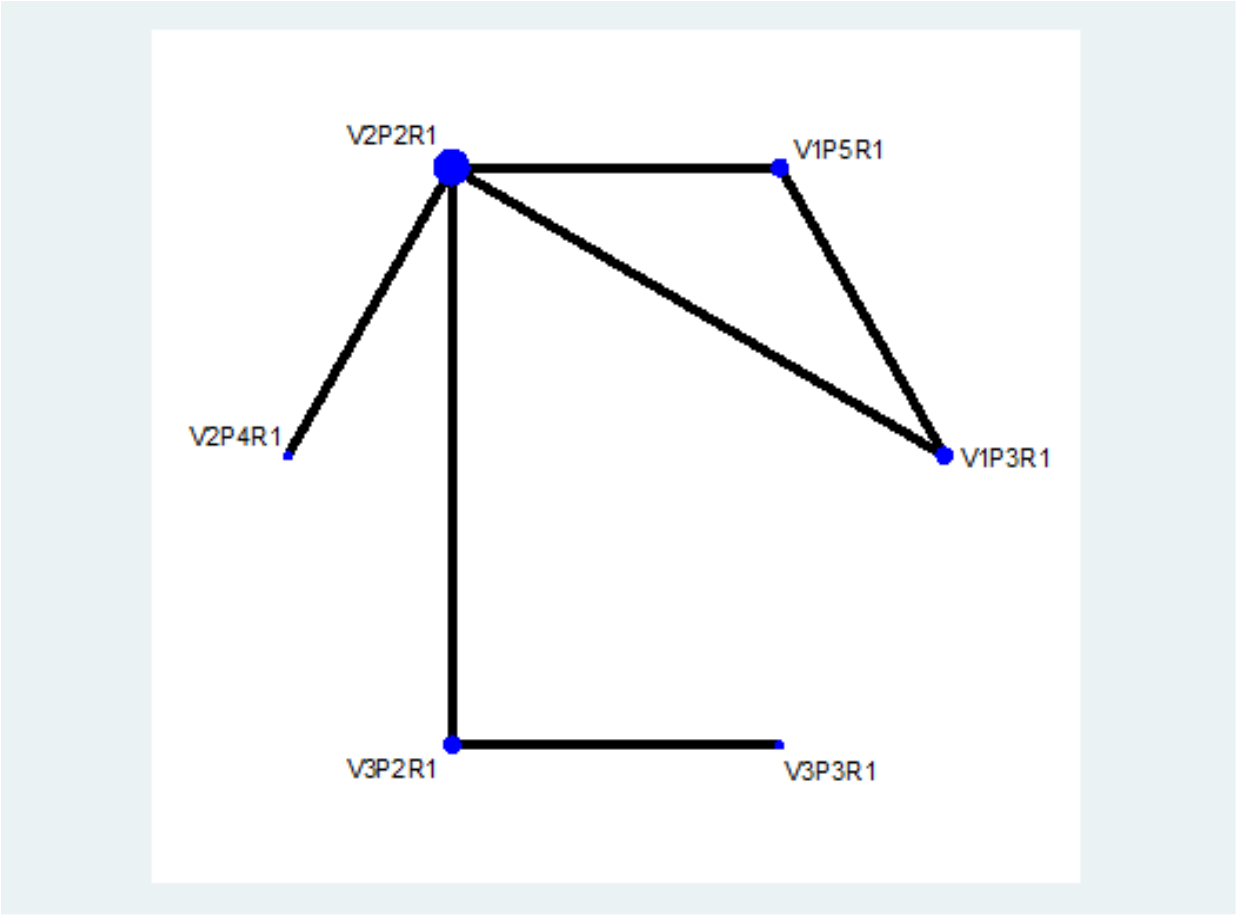


Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

6.3.5.7. ITU stay

Four trials (261 participants) provided data for the network meta-analysis on ITU stay.[242, 255, 258, 259] The other three trials did not report the ITU stay of their patients.[29, 256, 257] The network plot is shown in Figure 6.23. The results and model-fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model is provided in Table 6.34. The between-study standard deviation (tau) was 0. As indicated in Table 6.34, the fixed-effect model was preferred based on the DIC statistics. There was no evidence of inconsistency in the network. The pairwise MDs for the different treatment comparisons are shown in Table 6.35. As shown in Table 6.35, there is no evidence of any significant difference in ITU stay between the different treatments. As shown in Figure 6.24, none of the treatment strategies ranked best with more than 90% probability. Also, none of the treatment strategies ranked worst with more than 90% probability. As shown in Figure 6.25, V3P3R1 (intermittent vascular occlusion with CUSA and no fibrin) was within the three best treatments (of six treatments) with more than 90% probability. V3P2R1 (intermittent vascular occlusion with clamp-crush method and no fibrin) was within the four best treatments with a more than 90% probability. This suggests that these two treatment strategies may be better than other treatment strategies with regards to ITU stay.

Figure 6.23: Network plot of the treatment strategies for the outcome ITU stay.



Footnotes: circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Table 6.34: Results and model fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model for the outcome ITU stay

	Fixed effect model	Random-effects model	Inconsistency model (random-effects)
d[2]	0 (95% CI -3.32 to 3.33)	-0.01 (95% CI -6.56 to 6.55)	-
d[3]	0.01 (95% CI -3.32 to 3.34)	-0.01 (95% CI -6.55 to 6.53)	-
d[4]	0.01 (95% CI -4.69 to 4.71)	-0.01 (95% CI -9.27 to 9.24)	-
d[5]	-2.18 (95% CI -6.38 to 2.01)	-2.2 (95% CI -11.19 to 6.79)	-
d[6]	-3.68 (95% CI -9.04 to 1.68)	-3.7 (95% CI -14.81 to 7.41)	-
Dbar	27.07	27.07	27.07
pD	9	9	9
DIC	36.07	36.07	36.06

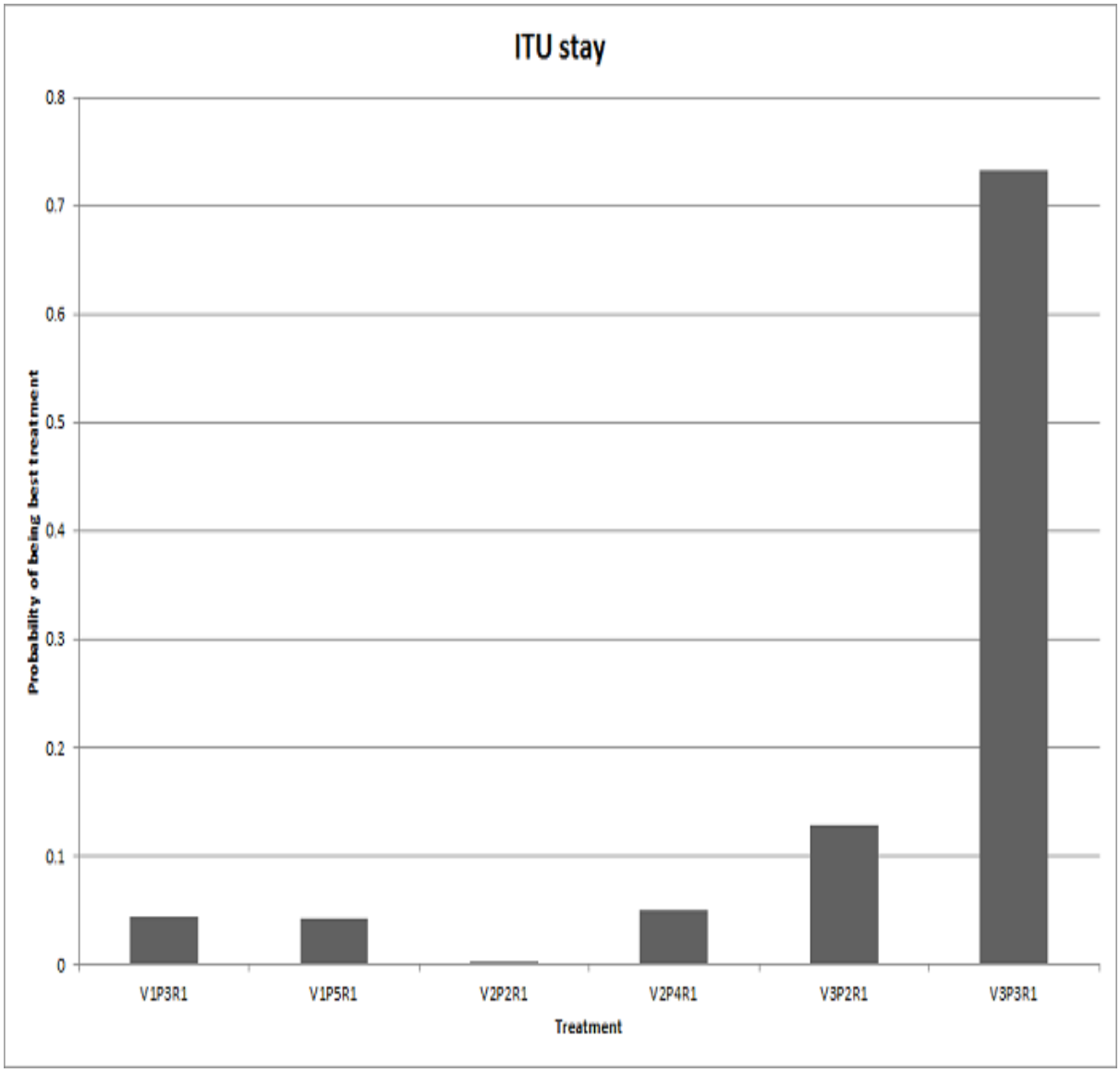
Footnotes: d[2] indicates the log odds ratio between treatment 2 and treatment 1, d[3] indicates the log odds ratio between treatment 3 and treatment 1, etc.; Dbar indicates the posterior mean of the residual deviance; pD indicates the effective number of parameters (leverage); DIC indicates the 'Deviance Information Criterion'. A lower Dbar indicates a better model fit. However, a model with lower DIC is generally chosen to aid better interpretation as it takes the model complexity into account. A lower DIC indicates a better model fit. Differences of less than 3 to 5 between the models are not considered important. Based on the information, fixed-effect model is the preferred model. There is no evidence of inconsistency since the difference in DIC between consistency and inconsistency models was not significant.

Table 6.35: Pairwise mean differences of the different treatment comparisons for the outcome ITU stay. There is no evidence of any significant difference in ITU stay between the different treatments.

	V1P5R1	**V2P2R1**	**V2P4R1**	**V3P2R1**	**V3P3R1**
V1P3R1	MD 0; 95% CI -3.32 to 3.33	MD 0.01; 95% CI -3.32 to 3.34	MD 0.01; 95% CI -4.69 to 4.71	MD -2.18; 95% CI -6.38 to 2.01	MD -3.68; 95% CI -9.04 to 1.68
V1P5R1	-	MD 0.01; 95% CI -4.7 to 4.71	MD 0.01; 95% CI -5.75 to 5.76	MD -2.19; 95% CI -7.54 to 3.17	MD -3.68; 95% CI -9.99 to 2.62
V2P2R1	-	-	MD 0; 95% CI -5.76 to 5.76	MD -2.19; 95% CI -7.55 to 3.16	MD -3.69; 95% CI -10 to 2.62
V2P4R1	-	-	-	MD -2.19; 95% CI -8.49 to 4.11	MD -3.69; 95% CI -10.82 to 3.44
V3P2R1	-	-	-	-	MD -1.5; 95% CI -8.3 to 5.31

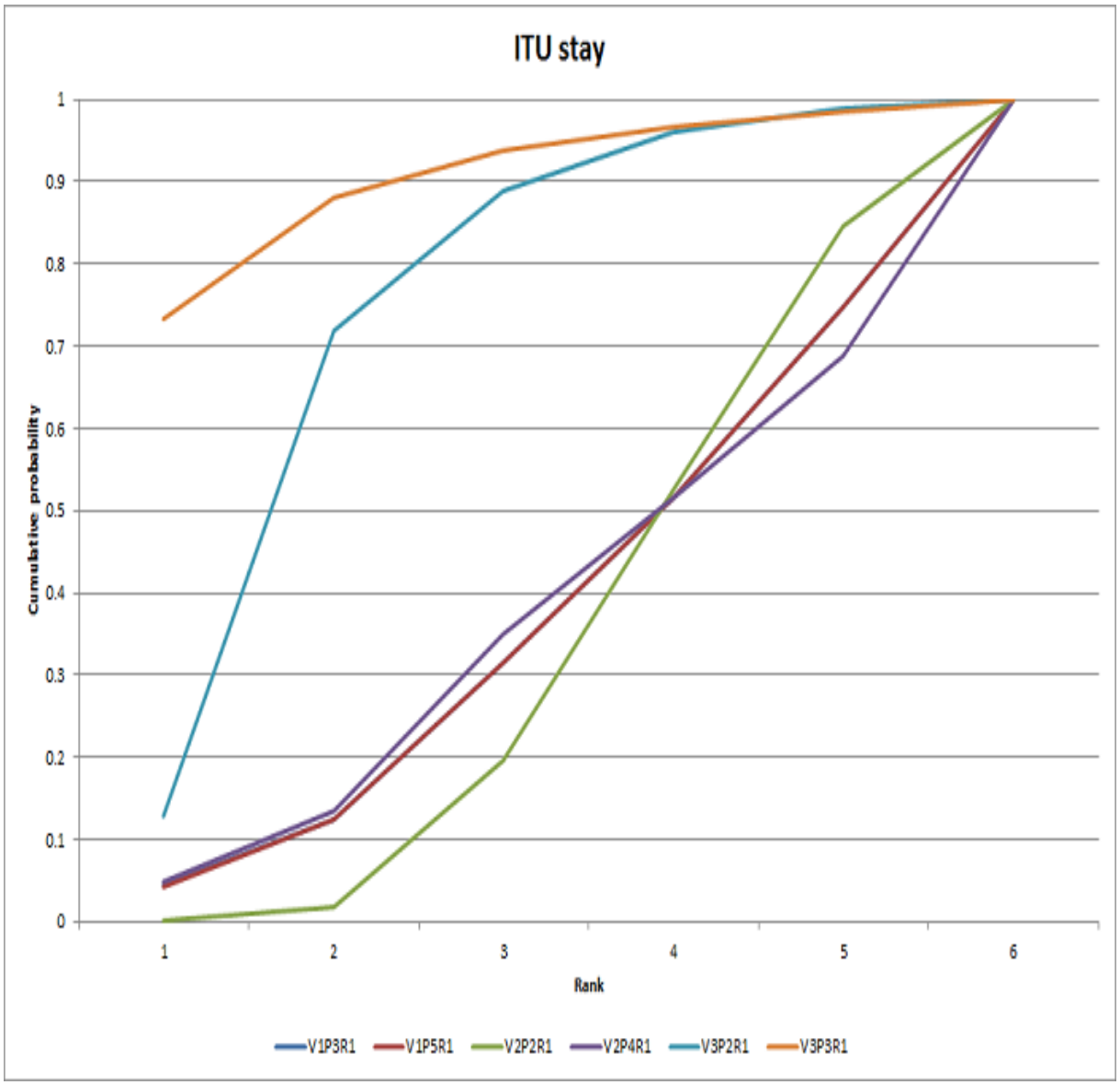
Footnotes: MD=mean difference; 95% CI=95% confidence intervals; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.24: Probability of being best treatment strategy for the outcome ITU stay. None of the treatment strategies ranked best with more than 90% probability.



Footnotes: V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.25: Cumulative probability of ranks of different treatments for the outcome ITU stay. V3P3R1 was within the three best treatments (of six treatments) with more than 90% probability. V3P2R1 was within the four best treatments with a more than 90% probability. This suggests that these two treatment strategies may be better than other treatment strategies with regards to ITU stay.

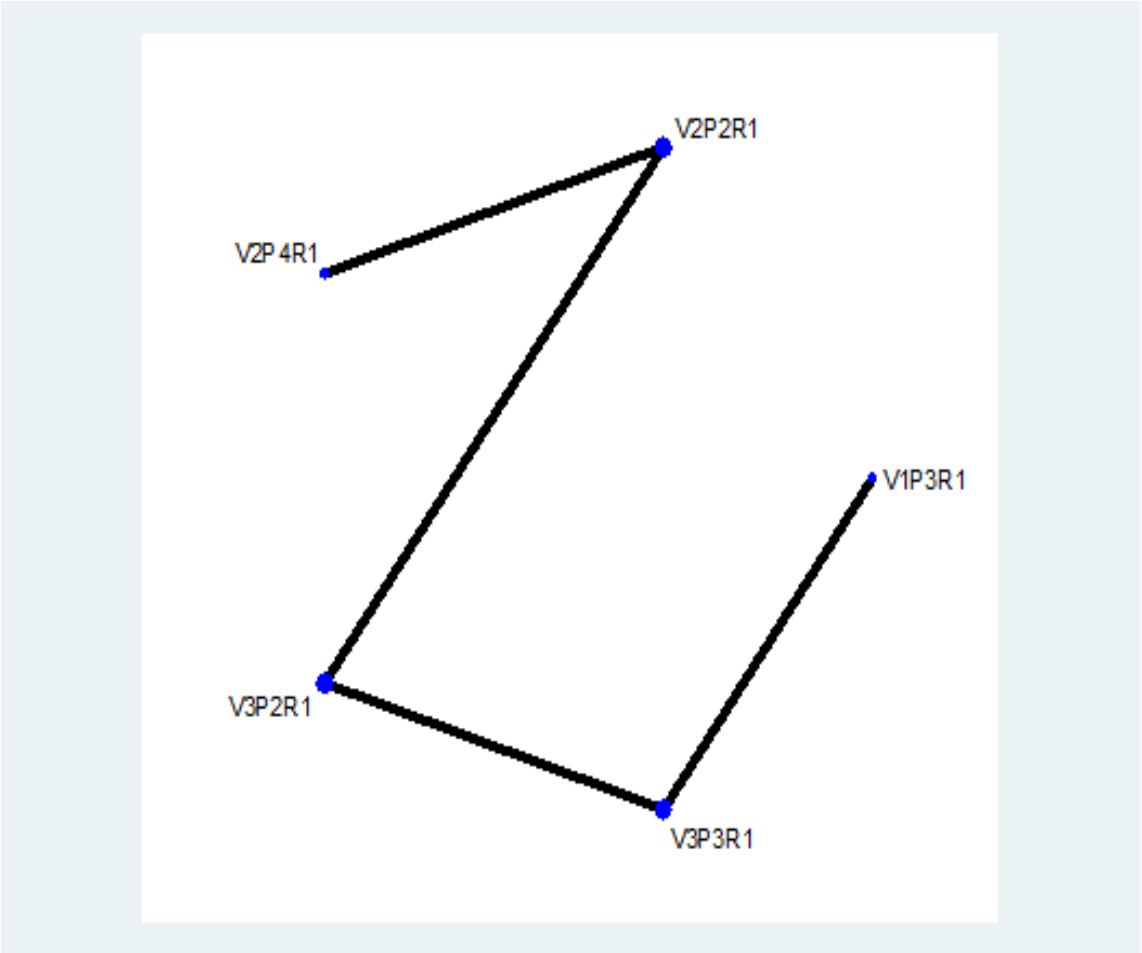


Footnotes: V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

6.3.5.8. Operating time

Five trials reported on operating time.[242, 256-259] The other two trials did not report the operating time of their patients.[29, 255] One trial[256] reporting on operating time had to be excluded from the analysis of this outcome because the treatment strategies it reported on were not directly compared with the treatment strategies of the other trials reporting on this outcome (i.e. not connected to the network plot for this outcome). Therefore, four trials (245 participants) provided data for the network meta-analysis on operating time.[255, 257-259] The network plot for this outcome is shown in Figure 6.26. The results and model-fit of the fixed-effect model and random-effects model along with the model-fit of the inconsistency model is provided in Table 6.36. The between-study standard deviation (tau) was 0.01. As indicated in Table 6.36, the fixed-effect model was preferred based on the DIC statistics. The model-fit of the inconsistency model was not reported because there was no closed loop in the network. The pairwise MDs for the different treatment comparisons are shown in Table 6.37. As shown in Table 6.37, people undergoing liver resection by the V3P3R1 method (intermittent vascular occlusion with CUSA and no fibrin) had significantly longer operating time than people undergoing liver resection by V1P3R1 (no vascular occlusion with CUSA and no fibrin) (MD 49.61 min; 95% CrI 29.81 to 69.41). There is no evidence of any significant difference in the operating time between the other comparisons. As shown in Figure 6.27, none of the treatments ranked best with more than 90% probability. As shown in Figure 6.28, there is substantial uncertainty about the treatment strategy with least operating time. There is more than 90% probability that V1P3R1 (no vascular occlusion with CUSA and no fibrin), V2P2R1 (continuous vascular occlusion with clamp-crush method and no fibrin), and V3P2R1 (intermittent vascular occlusion with clamp-crush method and no fibrin) are within the four best treatments (of five treatments). There is substantial uncertainty about the best or worst treatment strategy for operating time.

Figure 6.26: Network plot of the treatment strategies for the outcome operating time.



Footnotes: circles represent the treatment strategy as a node in the network; size of circles represents the number of RCTs reporting on the treatment strategy; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison; V1P3R1=no vascular occlusion with CUSA and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Table 6.36: Results and model fit of the fixed-effect model and random-effects model for the outcome operating time. The model-fit of the inconsistency model was not reported because there was no closed loop in the network.

	Fixed-effect model	Random-effects model
d[2]	8.41 (95% CI -61.25 to 78.07)	7.94 (95% CI -62.15 to 78.03)
d[3]	10.42 (95% CI -74.02 to 94.86)	9.33 (95% CI -75.48 to 94.14)
d[4]	7.25 (95% CI -47.15 to 61.64)	6.83 (95% CI -47.78 to 61.43)
d[5]	49.61 (95% CI 29.81 to 69.41)	49.35 (95% CI 28.83 to 69.87)
Dbar	67.38	67.4
pD	7.47	7.5
DIC	74.85	74.9

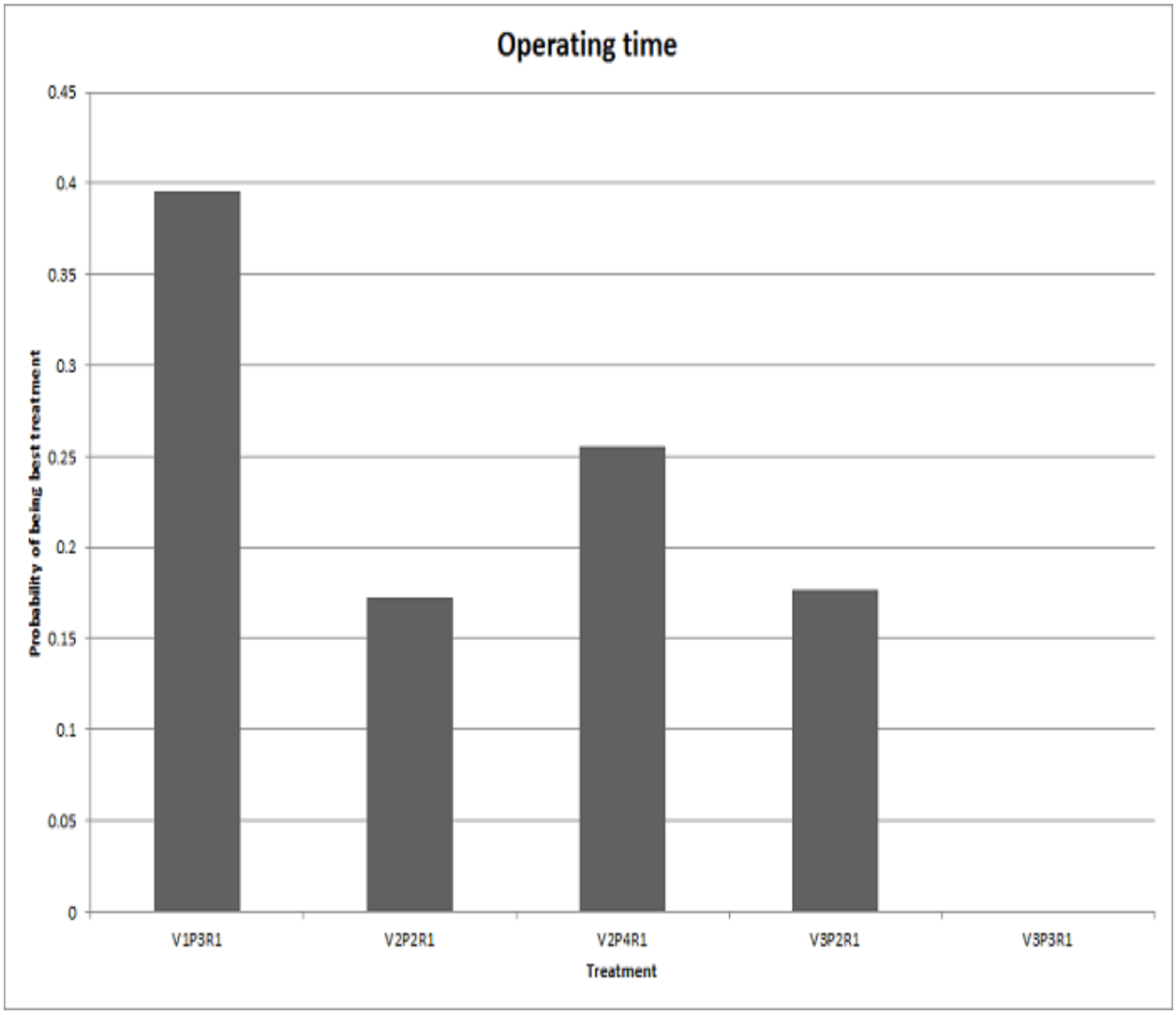
Footnotes: d[2] indicates the log odds ratio between treatment 2 and treatment 1, d[3] indicates the log odds ratio between treatment 3 and treatment 1, etc.; Dbar indicates the posterior mean of the residual deviance; pD indicates the effective number of parameters (leverage); DIC indicates the 'Deviance Information Criterion'. A lower Dbar indicates a better model fit. However, a model with lower DIC is generally chosen to aid better interpretation as it takes the model complexity into account. A lower DIC indicates a better model fit. Differences of less than 3 to 5 between the models are not considered important. Based on the information, fixed-effect model is the preferred model.

Table 6.37: Pairwise mean differences of the different treatment comparisons for the outcome operating time. Statistically significant results are in bold. People undergoing liver resection by the V3P3R1 had significantly longer operating time than people undergoing liver resection by V1P3R1. There is no evidence of any significant difference in the operating time between the other comparisons.

	V2P2R1	**V2P4R1**	**V3P2R1**	**V3P3R1**
V1P3R1	MD 8.41; 95% CI -61.25 to 78.07	MD 10.42; 95% CI -74.02 to 94.86	MD 7.25; 95% CI -47.15 to 61.64	**MD 49.61; 95% CI 29.81 to 69.41**
V2P2R1	-	MD 2.01; 95% CI -107.45 to 111.47	MD -1.17; 95% CI -89.55 to 87.21	MD 41.2; 95% CI -31.22 to 113.61
V2P4R1	-	-	MD -3.18; 95% CI -103.61 to 97.26	MD 39.19; 95% CI -47.54 to 125.92
V3P2R1	-	-	-	MD 42.37; 95% CI -15.52 to 100.25

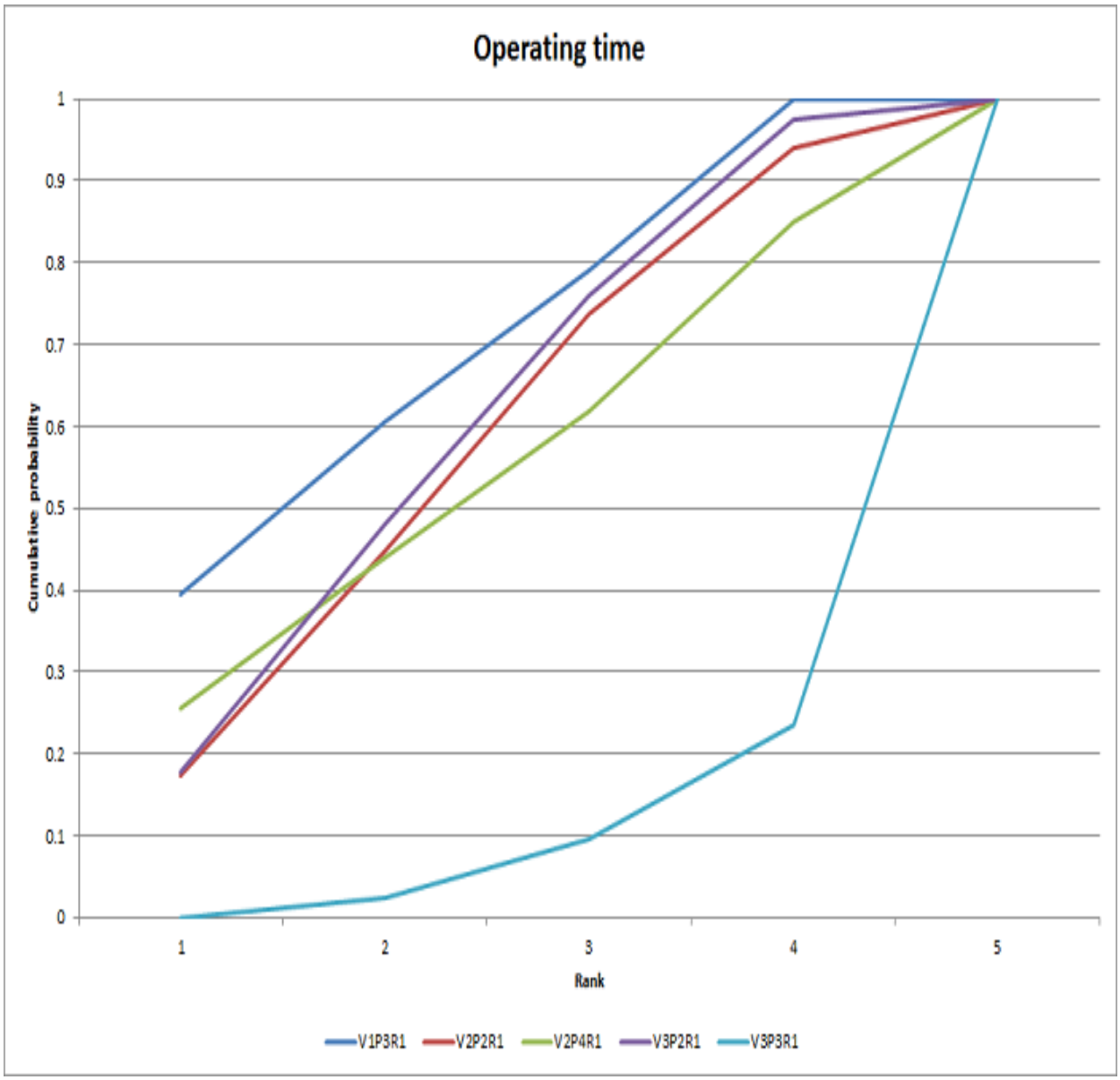
Footnotes: MD=mean difference; 95% CI=95% confidence intervals; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.27: Probability of being best treatment strategy for the outcome operating time. None of the treatments ranked best with more than 90% probability.



Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Figure 6.28: Cumulative probability of ranks of different treatments for the outcome operating time. There is more than 90% probability that V1P3R1, V2P2R1, and V3P2R1 are within the four best treatments (of five treatments). V3P3R1 has 76.4% probability of ranking the worst treatment strategy for operating time. There is substantial uncertainty about the best or worst treatment strategy for operating time.



Footnotes: V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

6.3.5.9. Outcomes not reported

None of the included trials reported on long-term mortality, quality of life, time needed to return to work, and the proportion of people who developed major blood loss. In one trial, two participants after undergoing liver resection with V2P4R1 (continuous vascular occlusion with sharp dissection and no fibrin sealant) were reoperated due to significant post-operative bleeding.[259] The authors stated that this was related to the sharp dissection method of parenchymal transection.[259] In another trial, one participant post hepatectomy with V1P3R1 (no vascular occlusion with CUSA and no fibrin sealant) underwent re-operation for significant post-operative bleeding.[257]

6.3.5.10. Summary of results

As shown in Figure 6.29, none of the treatments appear clearly superior to others when all the outcomes are considered together. We did not give any specific weighting to the different outcomes. However, if serious adverse events are considered more important than all the outcomes other than mortality, V1P2R1 (no vascular occlusion with clamp-crush and no fibrin) and V3P2R1 (intermittent vascular occlusion with clamp-crush and no fibrin) are better than the other treatment strategies with regards to serious adverse events. V1P5R1 (no vascular occlusion with radiofrequency dissecting sealer and no fibrin) and V2P2R1 (continuous vascular occlusion with clamp-crush and no fibrin) appear to be the worse in terms of serious adverse events. On the other hand, V2P2R1 (continuous vascular occlusion with clamp-crush and no fibrin) was the best treatment with regard to operative blood loss. There does not seem to be much correlation between a treatment being best in reducing blood loss and blood transfusion and being best in reducing serious adverse events and mortality. V3P3R1 (intermittent vascular occlusion with CUSA and no fibrin) provided the best results with regards to hospital stay and ITU stay.

All statistically significant results of the pairwise comparisons of the different treatment strategies for all outcomes of interest are shown in Table 6.38. The treatment strategies with the highest probability of ranking from best to worst (1st to 7th) for the outcomes of interest are summarised in Table 6.39.

Figure 6.29: Rankogram showing the probability that a treatment strategy is best for each outcome.

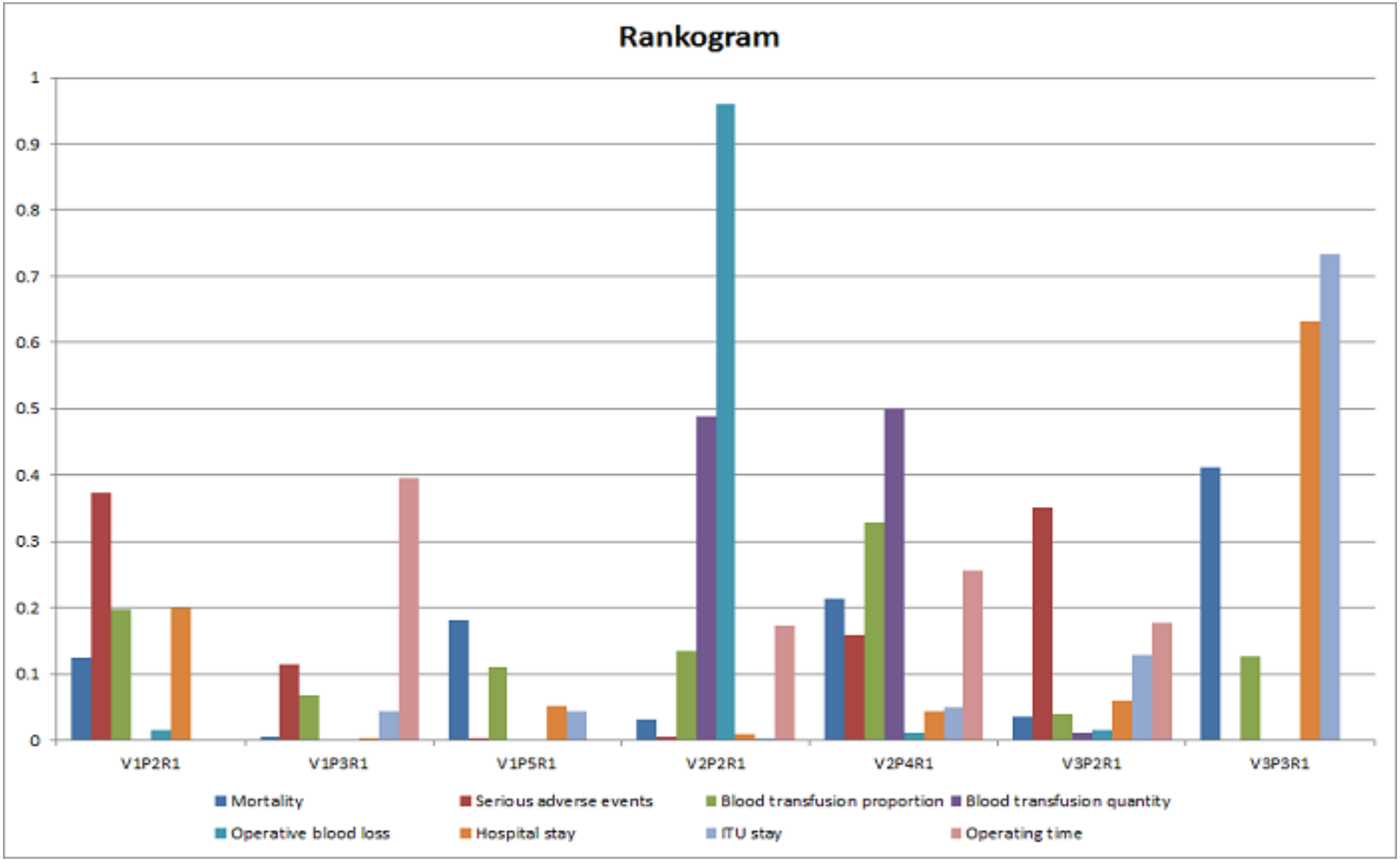


Table 6.38: Statistically significant pairwise odds ratios (yellow treatment over blue treatment) and mean differences (yellow treatment minus blue treatment) of the different treatment strategy comparisons for all outcomes of interest. There was no statistically significant difference between the treatment strategies for the outcomes: mortality, proportion of patients transfused, length of hospital stay, and ITU stay. Statistically significant results were reported for the outcomes: [1]=serious adverse events; [2]=quantity of blood transfusion; [3]= operative blood loss; [4]=operating time.

TREATMENT STRATEGIES	V1P3R1	V1P5R1	V2P2R1	V2P4R1	V3P2R1	V3P3R1
V1P2R1	NO	OR 7.13 (1.77 to 28.65)[1]	MD -130.9 (-255.89 to -5.91)[3]	NO	NO	NO
V1P3R1	NA	NO	NO	NO	NO	MD 49.61 (29.81 to 69.41)[4]
V1P5R1	NA	NA	NO	NO	NO	NO
V2P2R1	NA	NA	NA	NO	MD 1.2 (0.08 to 2.32)[2]	NO
V2P4R1	NA	NA	NA	NA	NO	NO
V3P2R1	NA	NA	NA	NA	NA	NO

Footnotes: OR=odds ratio; MD=mean difference; (95% credible intervals); NA=not applicable; NO=no statistically significant outcomes for this pairwise comparison; V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

Table 6.39: Treatment strategies with the highest probability of ranking from best to worst (1st to 7th) for the outcomes of interest.

TREATMENT STRATEGIES	RANKS						
	1st	2nd	3rd	4th	5th	6th	7th
Mortality	V3P3R1 P=0.412	V3P3R1 P=0.236	V3P2R1 P=0.236	V2P2R1 P= 0.203	V2P2R1 P= 0.270	V1P3R1 P=0.275	V1P3R1 P= 0.469
Serious adverse events	V1P2R1 P=0.373	V1P2R1 P=0.401	V1P3R1 P=0.295	V2P2R1 P=0.350	V2P2R1 P=0.346	V1P5R1 P=0.427	NA 1
Proportion of patients transfused	V2P4R1 P=0.328	V2P2R1 P=0.262	V2P2R1 P=0.216	V1P5R1 P=0.181	V3P2R1 P=0.214	V3P2R1 P=0.244	V3P3R1 P=0.339
Quantity of blood transfusion	V2P4R1 P=0.450	V2P2R1 P=0.502	V3P2R1 P=0.902	NA 2	NA	NA	NA
Operative blood loss	V2P2R1 P=0.960	V1P2R1 P=0.382	V1P2R1 P=0.451	V2P4R1 P=0.621	NA 3	NA	NA
Length of hospital stay	V3P3R1 P=0.633	V1P2R1 P=0.338	V3P2R1 P=0.363	V1P3R1 P=0.211	V2P2R1 P=0.296	V2P2R1 P=0.299	V2P4R1 P=0.465
ITU stay	V3P3R1 P=0.733	V3P2R1 P=0.589	V2P4R1 P=0.215	V1P3R1 P=0.202	V2P2R1 P=0.319	V2P4R1 P=0.312	NA 4
Operating time	V1P3R1 P=0.395	V3P2R1 P=0.304	V2P2R1 P=0.287	V2P4R1 P=0.230	V3P3R1 P=0.764	NA 5	NA

Footnotes: P=probability of ranking; NA=not applicable because less than 7 treatments were analysed for this outcome;
Treatment strategies not included in the analysis for individual outcomes of interest: 1=V3P3R1; 2=V1P2R1, V1P3R1, V1P5R1, V3P3R1; 3=V1P3R1, V1P5R1, V3P3R1; 4=V1P2R1; 5=V1P2R1, V1P5R1;
V1P2R1=no vascular occlusion with clamp-crush and no fibrin; V1P3R1=no vascular occlusion with CUSA and no fibrin; V1P5R1=no vascular occlusion with radiofrequency dissecting sealer and no fibrin; V2P2R1=continuous vascular occlusion with clamp-crush and no fibrin; V2P4R1=continuous vascular occlusion with sharp dissection and no fibrin; V3P2R1=intermittent vascular occlusion with clamp-crush and no fibrin; V3P3R1=intermittent vascular occlusion with CUSA and no fibrin.

6.4 DISCUSSION

This is the first network meta-analysis comparing the common combination of techniques aimed at decreasing blood loss during liver resection. The advantages of a network meta-analysis have been discussed in section 3.1. Importantly, a network meta-analysis combines direct evidence within trials and indirect evidence across trials facilitating indirect comparisons of multiple interventions that have not been studied in a head-to-head fashion. Therefore, a network meta-analysis provides estimates of effect sizes for all possible pairwise comparisons that may or may not have been evaluated directly against each other, and allows inferences into the comparative effectiveness of different treatments to be assessed even if they have not been compared directly in individual RCTs. This advantage of a network meta-analysis, allowed, in the current study, the comparison of different treatment strategies aiming to decrease blood loss during liver resection which have not been compared directly in trials before.

Another novel aspect of this study is the method of combining interventions aiming to decrease blood loss during liver resection, which is a new method of addressing the problem and can be used in future trials. In order to decrease blood loss during elective liver resection, a surgeon may use a particular combination of the different methods of vascular occlusion, of the different methods of parenchymal transection, and of the different methods of dealing with the raw surface of the liver after transection. Together, one can consider this combination of interventions as a treatment strategy. There have been no previous studies which attempted to address the problem of blood loss during liver resection, through comparison of treatment strategies defined by set criteria as in the current study. Future studies comparing interventions aiming to decrease blood loss during liver resection should attempt to follow this approach of combining interventions aiming to decrease blood loss into clearly defined treatment strategies for comparison.

Many published trials did not follow this approach and did not clearly define the method of vascular occlusion, parenchymal transection, and dealing with the raw surface in their trials. This resulted in the high number of excluded trials, and in the difficulty in identifying trials which would meet the inclusion criteria. Thirty six RCTs which included comparisons of one aspect of different methods of vascular occlusion or parenchymal transection or management of cut surface, had to be excluded because one

or more aspects of methods of vascular occlusion or parenchymal transection or management of cut surface not being compared were either not stated or were chosen in a non-random manner.[67, 70, 243, 245, 247, 253, 293-322] An important concern is the source of bias of those RCTs excluded, which did not clearly state on one or more aspects of methods of vascular occlusion or parenchymal transection or management of the liver cut surface. Also, if any of these three methods were chosen in a non-random manner, it would remove the element of randomisation of a trial meant to be a RCT, and would introduce selection bias into the trial. It is recommended that researchers performing future trials to investigate interventions aiming to decrease blood loss during liver resection should take this source of bias into consideration in order to minimise their study bias.

Due to the few trials that could be included for network meta-analysis in this review and the sparsity of data, the individual interventions included in the treatment strategies had to be revised into fewer categories by comparing only three methods of vascular occlusion (no vascular occlusion, continuous vascular occlusion, or intermittent vascular occlusion) and by having only two methods of treatment of the cut surface (fibrin sealant used or no fibrin sealant used). Nine RCTs met the inclusion criteria,[29, 242, 253-259] but only seven trials contributed data for the network meta-analysis.[29, 242, 255-259] This is because four treatment strategies in two trials were not connected to the network in any of the outcomes. In addition, one arm of a three-arm trial,[242] and one arm of a four-arm trial[255] had to be excluded because the methods of parenchymal transection used in these trials (parenchymal transection using bipolar cautery and water jet, respectively) were not included in this review. Furthermore, the treatment strategies from the trials that used fibrin sealant for management of the raw liver surface could not be connected to the network for any outcomes. Thus, the trials included in the network meta-analysis varied only in their approaches to vascular exclusion and parenchymal transection, and none used fibrin sealant. This is one of the disadvantages of a network meta-analysis, which can only compare treatments which are connected through a network plot.

Seven trials contributed data for the network meta-analysis,[29, 242, 255-259], including 496 participants randomised to seven different treatment strategies. Overall, no major advantage of one combination of techniques was identified over another, and none of the treatment strategies showed persistently poor outcomes. It was noted that some end

points could be worse and some better with any particular treatment strategy. There was no significant difference in mortality between the different treatment strategies. Mortality was generally low in all the groups compared to that reported in previous studies.[330] This may be because of the careful selection of participants included in RCTs compared to a consecutive case series[330] where the results of all liver resections were reported. There was no evidence to suggest that patients of lower anaesthetic risk were selectively recruited in the included RCTs.

It is not surprising that a significant reduction in mortality was not demonstrated by any of the treatment combinations. Even when the strategies are compared with the mortality of 3.5% observed in consecutive published series of liver resection for CLM,[330] to achieve a 20% relative reduction in mortality (20% relative risk reduction) from 3.5% to 2.8%, for a single comparison 20,116 participants are required based on type I error of 5%, and type II error of 20%. The number of participants compared between treatment strategies in this network meta-analysis was 496. As discussed in section 3.2.1, network meta-analyses may be more prone to the risk of random errors than direct comparisons.[155] Accordingly, a greater sample size is required in indirect comparisons than direct comparisons.[156] The effective sample size in an indirect comparison involving just three treatments is only a fraction of the number of participants included in direct comparisons in trials. In the example shown in section 3.2.1, 10,000 (7,500 + 2,500) participants included in the indirect comparisons was equivalent to 1,876 participants in the absence of heterogeneity and 938 participants in the presence of moderate heterogeneity. Even without these calculations, it is possible to observe that the confidence intervals in this study were very wide, which means a significant benefit or harm cannot be ruled out by using different treatments. Given the number of participants required to show a significant benefit of treatment with relation to mortality and serious adverse events, trials of this magnitude are unlikely to be funded.

Regarding serious adverse events, V1P5R1 (no vascular occlusion with radiofrequency dissecting sealer and no fibrin) was found to have significantly more serious adverse events compared to V1P2R1 (no vascular occlusion with clamp-crush and no fibrin). In more simple terms, serious adverse events were significantly higher with radiofrequency dissecting sealer compared to clamp-crush method in the absence of vascular occlusion or use of fibrin. Also, there was a high probability that V1P2R1 (no

vascular occlusion with clamp-crush and no fibrin) and V3P2R1 (intermittent vascular occlusion with clamp-crush and no fibrin) treatment strategies were better than other treatments with regards to serious adverse events. However, based on wide credible intervals, there was considerable uncertainty about the benefit of these methods over the methods other than radiofrequency dissecting sealer. Furthermore, the use of these treatment strategies was not justified by any of the other outcomes reported. None of these treatments significantly reduced ITU or hospital stay, which would be anticipated if an intervention made a significant reduction in serious adverse events. The network meta-analysis found no evidence of any significant difference in the length of hospital stay or ITU stay between any of the different treatment strategies. V3P3R1 (intermittent vascular occlusion with CUSA and no fibrin) which had the best outcomes with regards to hospital stay and ITU stay, was not included in the analysis for serious adverse events.

Intraoperative haemorrhage remains one of the major risks during liver resections, and operative blood loss and perioperative blood transfusion are two of the most important factors related to perioperative morbidity and mortality.[45, 46, 64, 65] People undergoing liver resection by V2P2R1 (continuous vascular occlusion with clamp crush method and no fibrin) were found to have significantly lower blood loss than those undergoing liver resection by V1P2R1 (no vascular occlusion with clamp-crush method and no fibrin). Importantly, V2P2R1 (continuous vascular occlusion with clamp-crush method and no fibrin) was ranked the best treatment with regards to operative blood loss with more than 90% probability.

The current review found no significant difference between the different treatment strategies in the proportion of people transfused. There was a significant difference in the amount of blood transfusion though, with people undergoing liver resection by V3P2R1 (intermittent vascular occlusion with clamp-crush method and no fibrin) having significantly higher amounts of blood transfused than people undergoing liver resection by V2P2R1 (continuous vascular occlusion with clamp-crush method and no fibrin). This result would support the finding of the previous paragraph, that liver resection under continuous vascular occlusion with clamp-crush and no fibrin, results in lower operative blood loss, and therefore, lower blood transfusion requirements.

Despite the statistically significant decrease in operative blood loss and in the amount of blood transfusion, V2P2R1 (continuous vascular occlusion with clamp-crush method and no fibrin) did not result in a statistically significant decrease in mortality, serious adverse events, hospital stay, and ITU stay. Therefore, the decrease in operative blood loss and blood transfusion may not be important on the background of no difference in clinical outcomes. On the other hand, there may not have been enough patients included in the analysis to detect statistical significance of such possible benefit in the clinical outcomes reported. There may be a cost benefit from the decrease in blood loss by resulting in a decreased need in blood transfusion. Furthermore, operative blood loss and perioperative blood transfusion may be used as surrogates for outcome after liver resection since it has been demonstrated in the literature that they are two of the most important factors affecting perioperative morbidity and mortality.[45, 46, 64, 65]

Regarding operating time, people undergoing liver resection by the V3P3R1 method (intermittent vascular occlusion with CUSA and no fibrin) had significantly longer operating time than people undergoing liver resection by V1P3R1 (no vascular occlusion with CUSA and no fibrin). This may have an impact on cost effectiveness on the background of no benefit in clinical outcomes. Moreover, none of the trials reported the quality of life. Quality of life is an important outcome used in assessing the cost-effectiveness of a treatment in a state-funded healthcare system. Given that the quality of life would depend upon various factors including peri-operative complications, length of hospital stay, and time to return to work, it is likely to be easier to demonstrate a significant difference in the quality of life if the treatment was effective than to demonstrate a difference in mortality or serious adverse events. Future RCTs should attempt to use a validated quality of life measure to compare treatments aiming to decrease operative blood loss.

This is the first network meta-analysis comparing methods aiming to decrease blood loss during elective liver resection. Previous pairwise meta-analyses compared individual components and concluded that intermittent vascular occlusion may decrease blood loss,[66] and that the clamp-crush method may decrease blood loss.[248] In this review, there was no evidence for any significant advantage of different methods of liver resection, and the best or worst treatment strategy aiming to decrease blood loss and blood transfusion could not be identified with confidence. The differences in conclusion with previous published reviews may be because of the exclusion of trials in

which the methods were not reported or when the other aspects of liver resection other than the component being compared were chosen in a non-random manner.

The major purpose of different methods of liver resection analysed in this review is to decrease the blood loss and blood transfusion requirements. Various methods have been proposed to achieve this. Some methods do not require any additional equipment (e.g., vascular occlusion), while other methods require special equipment (e.g., CUSA or radiofrequency dissecting sealer). This review has shown that simple methods, such as clamp-crush method, do not appear to result in poorer outcomes than other methods which require special equipment. In addition, this review has suggested that special equipment like the radiofrequency dissecting sealer may actually result in higher morbidity. These results may have important financial implications, and they are useful for clinicians and managers, in planning treatment for patients with CLM and in minimising expenses in a state-funded healthcare system with limited resources.

Caution is needed when interpreting the results of this network meta-analysis due to the low number of trials and participants included. Also, caution is needed due to the possible sources of heterogeneity and bias of the included trials. There was no significant heterogeneity in all the outcomes other than proportion of blood transfused as indicated by the good model-fit achieved by fixed-effect model as compared to the random-effects model. The effect estimates were wide with the credible intervals overlapping 1 and with either 20% reduction (0.80) or 20% increase (1.20) which can be considered a clinically significant effect. Future trials should be adequately powered to decrease the risk of random errors.

Clinical and methodological heterogeneity was also assessed by carefully examining the characteristics and design of included trials. Major sources of clinical heterogeneity included cirrhotic compared to non-cirrhotic livers, and major compared to minor liver resections. A large variation in the proportion of major liver resections performed and the proportion of cirrhotic livers included in the different treatment strategies compared was identified (Table 6.18) and these may be a major source of clinical heterogeneity. Unfortunately, due to the low number of studies included in the analysis, a metaregression or sensitivity analysis based on the number of major hepatectomies or cirrhotic livers, could not be performed.

In addition, considerable heterogeneity was anticipated in the way the interventions aiming to decrease blood loss were performed. For example, intermittent portal triad clamping may be performed with different time periods of occlusion and non-occlusion. Likewise, there was no distinction between different maximum periods for continuous vascular occlusion.[331] Also, for liver outflow obstruction, it was not determined whether the suprahepatic inferior vena cava or the hepatic veins were occluded. These practice variations might be a source of heterogeneity; however, evidence was insufficient to suggest that these variations may affect the outcome.

Moreover, the overall quality of evidence in this review was low. The risk of bias was high in all the included trials. Using appropriate methods of randomisation and reporting the method of randomisation adequately will decrease selection bias. While the surgeons who perform the surgery cannot be blinded to the treatments, it is possible to blind the surgeons or healthcare provides who are involved in the day-to-day postoperative management of the patient and assess the postoperative outcomes of surgery. While it may be difficult to blind the anaesthetist to the treatment groups, using objective criteria for transfusion,[332] may overcome the problem of bias due to lack of blinding with regards to intra-operative blood transfusion. The intensivist involved in the post-operative care of the patient can be also blinded. Objective criteria for detection of complications along with the postoperative management of the patient by a healthcare team not involved in the operation can decrease detection and performance bias. With regards to drop-outs, randomising the participants after confirming that the tumour can be removed can avoid post randomisation drop-outs due to metastatic spread identified at the time of laparotomy. This can decrease attrition bias. In addition, reporting all the important clinical outcomes can decrease selective reporting bias.

It should be noted that ischaemic preconditioning was used prior to continuous vascular occlusion with a maximum continuous clamp period of 75 minutes in one trial,[258] and in the other trial ischaemic preconditioning was used in the second half of the trial.[259] Ischaemic preconditioning aims to decrease ischaemic-reperfusion injury, and is the temporary occlusion of vessels supplying the liver to ‘condition’ the liver to blood flow occlusion before exposing the liver to a prolonged period of blood flow occlusion during liver resection. Not controlling for the application of ischaemic preconditioning in a trial comparing methods aiming to decrease operative blood loss is a source of bias

or heterogeneity between studies, because ischaemic preconditioning itself may affect the operative blood loss.

6.5 CONCLUSIONS

Liver resection is a major surgery with significant mortality and morbidity, and various methods have been attempted to decrease blood loss, and therefore, morbidity during elective liver resection. This review assessed the comparative benefits and harms of different treatment strategies aiming to decrease operative blood loss, by combining the methods of vascular occlusion, parenchymal transection, and management of the cut surface of the liver that a surgeon would typically use during the operation. A significant number of RCTs had to be excluded by the analysis because they did not report on all three methods aiming to decrease operative blood loss. There was no difference in mortality between the treatment strategies, but there was an increase in the proportion of people with serious adverse events when surgery was performed using radiofrequency dissecting sealer compared with the standard clamp-crush method in the absence of vascular occlusion and fibrin sealant. People undergoing liver resection by intermittent vascular occlusion had higher amounts of blood transfused than people with continuous vascular occlusion when the parenchymal transection was carried out with the clamp-crush method and no fibrin sealant was used for the cut surface. Furthermore, people undergoing liver resection using continuous vascular occlusion had lower blood loss than people with no vascular occlusion when the parenchymal transection was carried out with clamp crush method and no fibrin sealant was used for the cut surface. There was no difference between treatment strategies in length of hospital stay or ITU stay. Overall, this network meta-analysis found no evidence to prefer one treatment strategy over another. Simple methods, such as clamp-crush method, appear to give equivalent outcomes to other methods which require special equipment. Further RCTs are required to compare methods aiming to decrease blood loss during liver resection taking into consideration the possible sources of bias and heterogeneity identified in this review.

CHAPTER 7

REVIEW OF THE LITERATURE TO ASSESS WHETHER NOT REPORTING THE PERIOD OF FOLLOW-UP IS A SOURCE OF BIAS IN TRIALS COMPARING LONG-TERM OUTCOMES

7.1 INTRODUCTION

Patients suffering with CLM need to be followed up for a period of years in order to determine their outcome and whether the treatment they received was optimal. This requirement for long-term follow up is the same for most types of cancer and many chronic diseases. To answer some of the important controversies in the management of CLM therefore requires long-term prospective clinical trials of the interventions. Trials comparing treatments for patients with CLM should follow-up these patients for a sufficiently long period of time in order to reach correct conclusions about the efficacy or adverse effects of these treatments. Survival and disease recurrence are the main outcomes when comparing treatments for CLM, and both require long term follow-up to determine which treatments are best. The optimal follow-up period in comparing treatments in patients with CLM with regards to survival benefit is not known. While following these patients for a long period will provide definitive answers, a long follow-up period will increase the trial costs and delay the adoption of treatment whereas a short period of follow-up may not be informative.

The follow up period required for cancer or a chronic disease is likely to be related to the natural history of the disease and its response to treatment. In breast cancer where survival overall is excellent but recurrence after 10 years is well described, then very long follow up to evaluate new cancer therapies is essential.[333-336] In the case of CLM, the median survival for untreated disease ranges between six to twelve months.[14, 15] Five-year survival for patients with CLM who undergo liver resection, ranges between 32 and 58%,[19-24, 26, 27, 161] and 10-year survival ranges between 22 and 28%.[20-22, 26, 27, 161] For patients with unresectable CLM, modern systemic neoadjuvant chemotherapy can be used to downsize the liver metastases so that an R-0 resection (negative tumour margins) is possible, and allows approximately 12.5% of patients with unresectable CLM to be rescued by liver surgery.[16, 28, 29] Furthermore, the use of modern adjuvant chemotherapy for patients with CLM who underwent liver resection with curative intent, may result in improvement of disease-free survival and overall survival.[30-34] Given that surgery for CLM produces a good 5-year survival, this is usually taken as the most important outcome measure for treatments of CLM.

An example where inadequate follow-up of participants gave an inappropriate answer to the treatment of patients undergoing liver resection for CLM was the European

Organization for Research and Treatment of Cancer (EORTC) intergroup trial 40983 (EPOC).[32] The EPOC trial demonstrated that perioperative FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) therapy (six cycles before surgery and six cycles after) significantly improved 3-year disease free survival compared with surgery alone for CLM.[32] After this trial was published, perioperative chemotherapy became the standard of care for patients with resectable CLM, especially in western countries.[337, 338] But, after a median follow-up of 8.5 years was carried out for the same trial, no significant survival advantage was demonstrated between the perioperative chemotherapy and the surgery alone groups.[339]

During the course of this thesis, it was noted that the period of follow-up was inadequately reported by trials comparing time-to-event outcomes for CLM. Chapter 4 of this thesis discussed whether to perform combined or sequential resection for synchronous CLM. Chapter 5 discussed the surgical management and survival of patients with CLM and positive hepatic lymph node metastases. For both chapters, the long-term outcomes mortality and disease recurrence were important to decide the best treatment for patients with CLM. In order to answer correctly the important clinical questions raised in both chapters, appropriate periods of follow-up were required by the included trials. However, from the studies included in Chapter 4, fourteen studies reported the period of follow-up of their participants and 10 studies did not report the period of follow-up. For Chapter 5, fourteen studies reported the length of follow-up and seven studies did not. Chapters 6 and Appendix of this thesis included trials assessing the short-term perioperative outcomes of different interventions aiming to decrease blood loss and blood transfusion during liver resection, and different interventions aiming to decrease ischaemic-reperfusion injury during liver resection. None of the included trials in Chapters 6 and Appendix reported the period of follow-up of the participants. Although the outcomes investigated in Chapters 6 and Appendix are perioperative short-term outcomes, an argument could be made that any perioperative interventions may have a long-term impact on survival and disease recurrence of patients with CLM, and the period of follow-up (and hence, reporting the period of follow-up) is important in these trials too. Recognising the importance of the duration of follow-up in trials comparing treatments for CLM, and recognising that the period of follow-up is not adequately reported in these trials, led to the current review.

There is a valid concern that that not reporting the overall period of follow-up by trials comparing time-to-event outcomes for CLM, would introduce significant bias in these trials. Researchers should always try to exclude known sources of bias in their trials, but they should also try to identify new possible sources of bias when designing trials. It is thought that adequately designed trials comparing treatments for CLM, or for any other type of cancer or chronic disease, should clearly report the period of follow-up of the participants in the trials. This is important when evaluating outcomes requiring long period of time to be assessed, such as survival and disease recurrence. Not reporting the period of follow-up may result in bias of the results of comparative trials.

There has been no previous study examining whether reporting or not reporting the length of follow-up, in comparative trials investigating time-to-event outcomes, is a potential source of bias. The method used in this study was to identify RCTs included in meta-analyses published in Cochrane, and compare the time-to-event outcomes of trials reporting versus trials not reporting the follow-up period of their participants.

7.1.1. Aims of this review

The aim of this review is to investigate whether not reporting the period of follow-up in comparative trials comparing time-to-event outcomes (survival, disease recurrence) of patients with CLM is a potential source of bias. In order to achieve this aim, the time-to-event outcomes of trials reporting versus trials not reporting the follow-up period of their participants were to be compared. Nevertheless, the number of RCTs published comparing time-to-event outcomes of patients with CLM is very limited to allow a meta-analysis to be performed.

Because of the limited number of RCTs comparing time-to-event outcomes of patients with CLM, in order to meet the aim of this review, RCTs included in meta-analyses published in Cochrane on any type of cancer were identified, and the time-to-event outcomes of trials reporting versus trials not reporting the follow-up period of their participants were compared.

7.2 METHODS

In summary, the methods used in this review to assess whether reporting the period of follow-up is a source of bias in trials comparing long-term outcomes were as follows:

- identify RCTs comparing long-term outcomes (survival and disease recurrence) included in meta-analyses published in the Cochrane Library
- for each meta-analysis identify which included RCTs reported and which RCTs did not report the period of follow-up
- for each meta-analysis compare the long-term outcomes found by RCTs reporting and not reporting the period of follow-up, and calculate a relative Hazard ratio (HR) for each meta-analysis
- combine the results of all meta-analyses to test if the long-term outcomes of studies reporting and not reporting the period of follow-up were significantly different

7.2.1 Search strategy

An electronic database search was performed of MEDLINE from PubMed to identify published Cochrane meta-analyses of RCTs that contained hazard ratio (HR) in their abstract or the outcome(s) that were meta-analysed were ‘disease recurrence’ and/or ‘survival’. Only MEDLINE from PubMed was searched because Cochrane reviews are all available in Pubmed. The latest date for this search was June 23, 2014.The following search strategy was used in MEDLINE: Cochrane Database Syst Rev [jo] AND (HR [tiab] OR hazard ratio*[tiab] OR mortality OR survival OR recurrence OR time-to) AND (2000[pdat] or 2001[pdat] or 2002[pdat] or 2003[pdat] or 2004[pdat] or 2005[pdat] 2006[pdat] or 2007[pdat] or 2008[pdat] or 2009[pdat] or 2010[pdat] or 2011[pdat] or 2012[pdat] or 2013[pdat]).

7.2.2 Inclusion and exclusion criteria

For studies to be included in this review, they should be meta-analyses of RCTs published by The Cochrane Collaboration between 2000 and 2013. The meta-analyses

published in Cochrane were selected because they were considered to be a reliable source of data for the included RCTs and allowed us to identify RCTs reporting on the same long-term outcomes. They should have reported on HR as the measure of effect for the outcomes disease recurrence or mortality (i.e. not used a different measure of effect, e.g. odds ratio, risk ratio, etc.). For a meta-analysis to be included in this review, at least two of its included trials should have reported the period of follow-up, and at least two of its included trials should have not reported the period of follow-up, in order to be able to compare the results of the trials reporting and not reporting follow-up for each meta-analysis included in this review.

7.2.3 Data extraction

From each Cochrane meta-analysis that met the inclusion criteria and for each individual RCT included in a meta-analysis that met the inclusion criteria, two review authors (Constantinos Simillis and Marios Zertalis) independently extracted the following data: name of first author, year of publication, language of publication, country and year(s) of conduct of the study, inclusion and exclusion criteria, sample size, study design, length of follow-up of the participants if reported, HR and Standard Error (SE) for disease recurrence and/or mortality. Any discrepancies between the two reviewers were resolved through discussion. The risk of bias of the meta-analyses or the individual trials was not assessed because it was not required for this review.

7.2.4 Outcomes of interest and definitions

For each meta-analysis the number of included RCTs reporting and not reporting the period of follow-up was identified. Each individual RCT, included in the meta-analyses, was checked to assess whether the period of follow-up for the patients included in the trial was reported or not reported. From individual RCTs the HR with 95% CI, lnHR, and SE(lnHR) for the time-to-event outcomes ‘Disease recurrence’ and ‘Mortality’ were collected.

7.2.5 Statistical analysis

From each meta-analysis included in this review, the trials that reported the period of follow-up and the trials that did not report the period of follow-up were identified. For each RCT included in a meta-analysis, the HR with 95% CI, lnHR (natural logarithm of hazard ratio), and SE(lnHR) (standard error of natural logarithm of hazard ratio) for the time-to-event outcomes 'Disease recurrence' and "Mortality" were collected. Analysis was conducted using Review Manager (RevMan) Version 5.1.[138]

RevMan was used to calculate the overall effect estimate HR, using inverse-variance method and a random-effects model, for 'Disease recurrence' and 'Mortality' of the trials within a meta-analysis that reported the period of follow-up. RevMan was similarly used to calculate the overall effect estimate HR for 'Disease recurrence' and 'Mortality' of the trials within the same meta-analysis that did not report the period of follow-up. Then, using indirect comparison calculations, the relative HR with 95% CI, lnHR, and SE(lnHR) were calculated for each meta-analysis, of the trials that reported follow-up period [HR of studies that reported follow-up] versus the trials that did not report the period of follow-up [HR of studies that did not report follow up].

Relative HR for each meta-analysis = [HR of studies that reported follow-up] / [HR of studies that did not report follow up]

The calculated relative HR for each meta-analysis was then inserted in RevMan to calculate the overall effect estimate of the relative HR with 95% CI of all the trials reporting period of follow-up versus the trials not reporting the period of follow-up for the outcomes 'Disease recurrence' and 'Mortality'. Again, inverse-variance method and a random-effects model were used. Statistical significance would suggest a difference in outcome between trials reporting period of follow-up and trials not reporting period of follow-up, and therefore, not reporting the period of follow-up period would be considered to be a source of bias in trials assessing time-to-event outcomes (mortality and disease recurrence).

Heterogeneity between meta-analyses was explored using the chi-squared test, with significance set at the $P<0.10$ level, and the amount of heterogeneity was determined by

means of I-square. Graphical exploration with funnel plots was used to evaluate publication bias.[145, 147] Also, sensitivity analysis was undertaken using the following subgroups: meta-analyses published after 2010, and meta-analyses including more 10 or more RCTs.

7.3 RESULTS

7.3.1 Eligible studies

A total of 3,295 references were identified following the search strategy described above. No more references were identified for further assessment through scanning reference lists of the identified studies. The duplicates excluded were 64. A further 3,085 clearly irrelevant references were excluded through screening titles and reading abstracts. The remaining 146 studies, which were Cochrane meta-analyses, were reviewed in detail. From the meta-analyses reviewed in detail, 125 meta-analyses were excluded because either less than two of their included trials reported the period of follow-up, or less than two of their included trials did not report the period of follow-up, or they did not report on HR as the measure of effect for the outcomes disease recurrence or mortality. In total, 21 meta-analyses[340-360] met the inclusion criteria and were included in this review. This is summarised in the study flow diagram in Figure 7.1. The 21 meta-analyses included in this review reported on 136 RCTs which included the follow-up period and 134 RCTs which did not include the follow-up period (Table 7.1).

Figure 7.1: Study flow diagram.

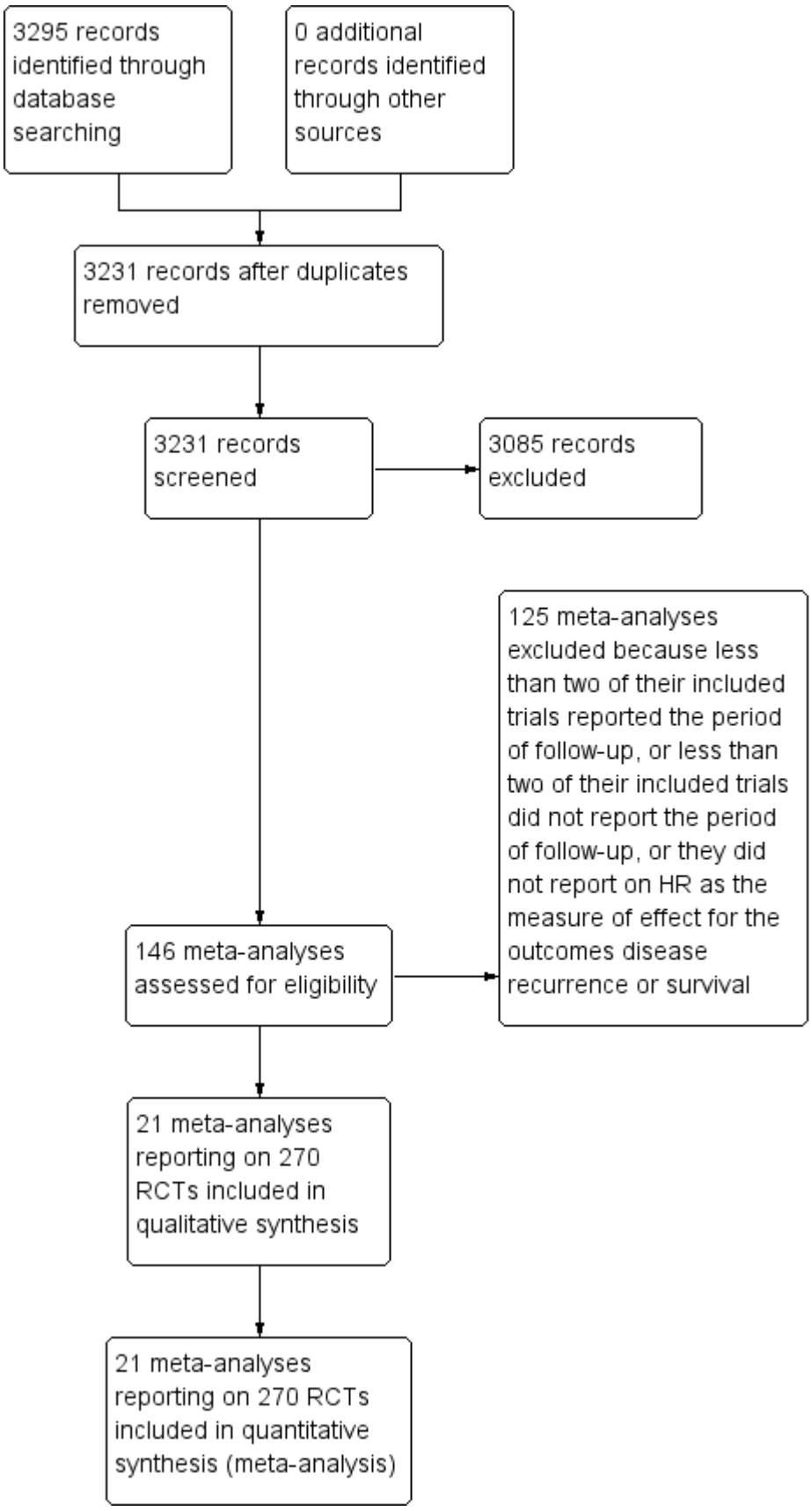


Table 7.1: Meta-analyses included in the review with their numbers of trials reporting or not reporting on the period of follow-up.

Cochrane meta-analysis first author	Year of publication of meta-analysis	Number of RCTs reporting period of follow-up	Number of RCTs not reporting period of follow-up
Arnott	2005	2	4
Bohlius	2008	5	5
Butters	2010	3	11
Carrick	2009	10	26
Diaz-Nieto	2013	17	17
Furness	2011	12	13
Gibson	2009	8	5
Glenny	2010	12	5
Mao	2012	2	2
Mocellin	2009	3	7
Mocellin	2013	15	2
O'Rourke	2010	5	4
Oliveri	2011	6	3
Pidala	2011	10	3
PORT	2005	5	3
Ronellenfitsch	2013	10	4
Rydzewska	2012	3	3
Steurer	2006	2	2
Vale	2012	2	6
van Dalen	2009	2	7
Wagner	2009	2	2

7.3.2 Overall results of meta-analysis

As an example, the analysis performed in this review for the meta-analysis by Diaz-Nieto *et al.*[344] is shown in Figures 7.2 to 7.9. Similar analysis to the one described here, was performed for all the 21 meta-analyses included in this review. Figure 7.2 shows the analysis of the RCTs included in the meta-analysis by Diaz-Nieto *et al.* that reported the period of follow-up for the outcome mortality. Figure 7.4 shows the analysis of the RCTs included in the meta-analysis by Diaz-Nieto *et al.* that did not report the period of follow-up for the outcome mortality. Figure 7.6 shows the analysis of the RCTs included in the meta-analysis by Diaz-Nieto *et al.* that reported the period of follow-up for the outcome disease recurrence, and Figure 7.8 shows the analysis of the RCTs that did not report the period of follow-up for the outcome disease recurrence. There was no evidence of significant publication bias in the analysis of the RCTs that reported the period of follow-up, and the RCTs that did not report the period of follow-up, for the outcomes mortality and disease recurrence, as shown in Figures 7.3, 7.5, 7.7, and 7.9.

Figure 7.2: Forest plot of the RCTs included in the meta-analysis by Diaz-Nieto *et al.*[344] that reported the period of follow-up for the outcome mortality. This forest plot shows that RCTs on adjuvant chemotherapy for gastric cancer reporting the follow-up period showed a significant benefit to adjuvant chemotherapy regarding survival.

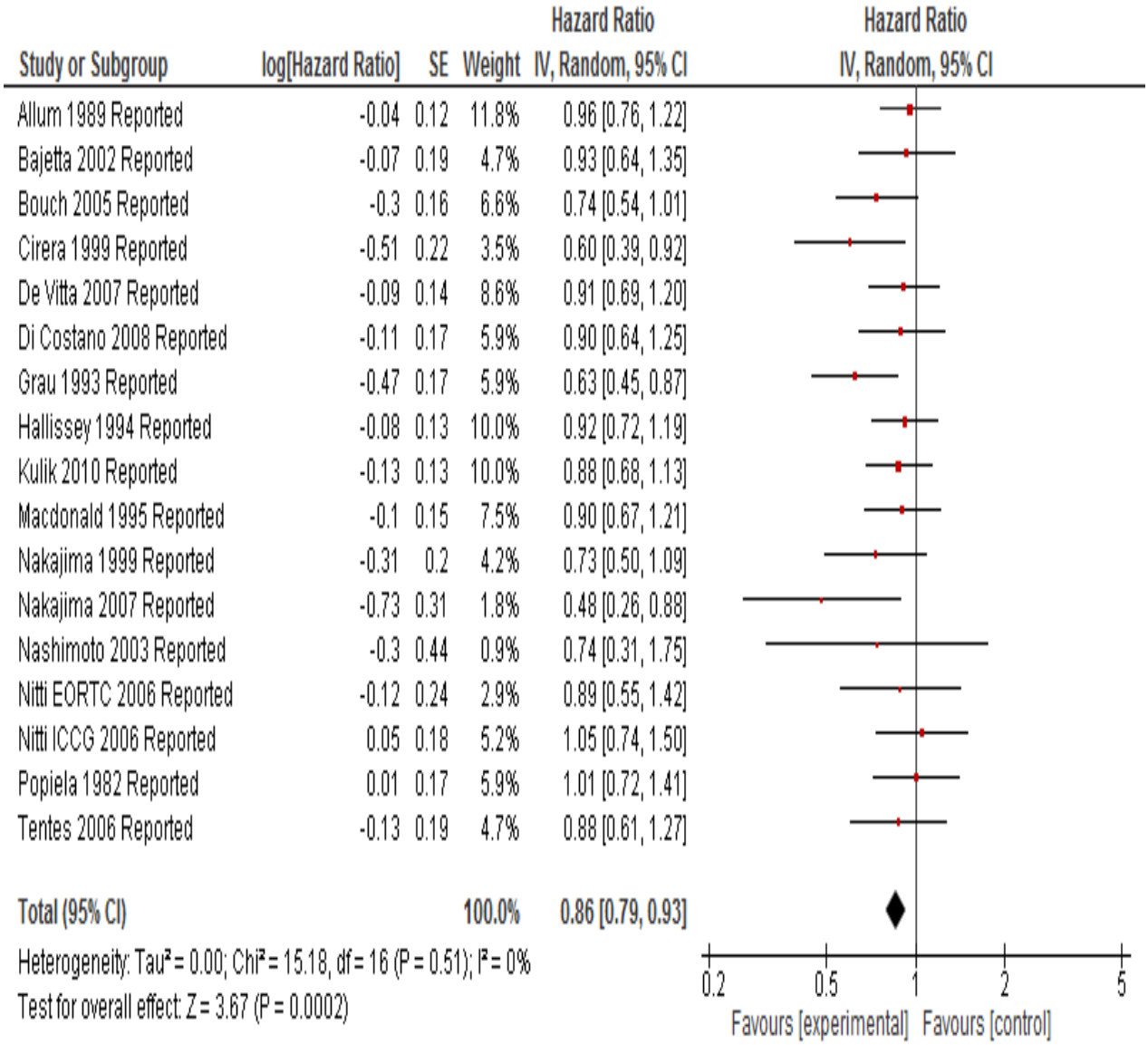


Figure 7.3: Funnel plot of the RCTs included in the meta-analysis by Diaz-Nieto *et al.*[344] that reported the period of follow-up for the outcome mortality. There was no evidence of significant publication bias in the analysis of the RCTs that reported the period of follow-up.

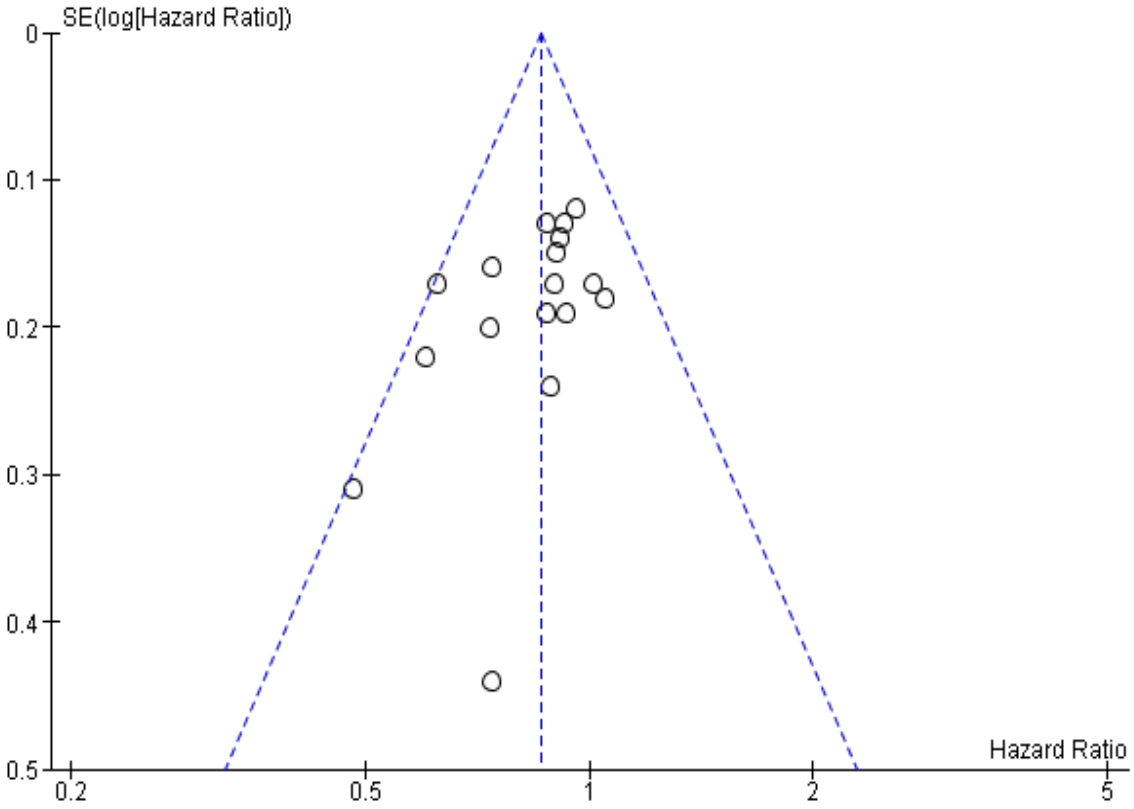


Figure 7.4: Forest plot of the RCTs included in the meta-analysis by Diaz-Nieto *et al.*[344] that did not report the period of follow-up for the outcome mortality. This forest plot shows that RCTs on adjuvant chemotherapy for gastric cancer not reporting the follow-up period showed a significant benefit to adjuvant chemotherapy regarding survival. These results are similar to Figure 8.2, for the RCTs in the same meta-analysis reporting the follow-up period

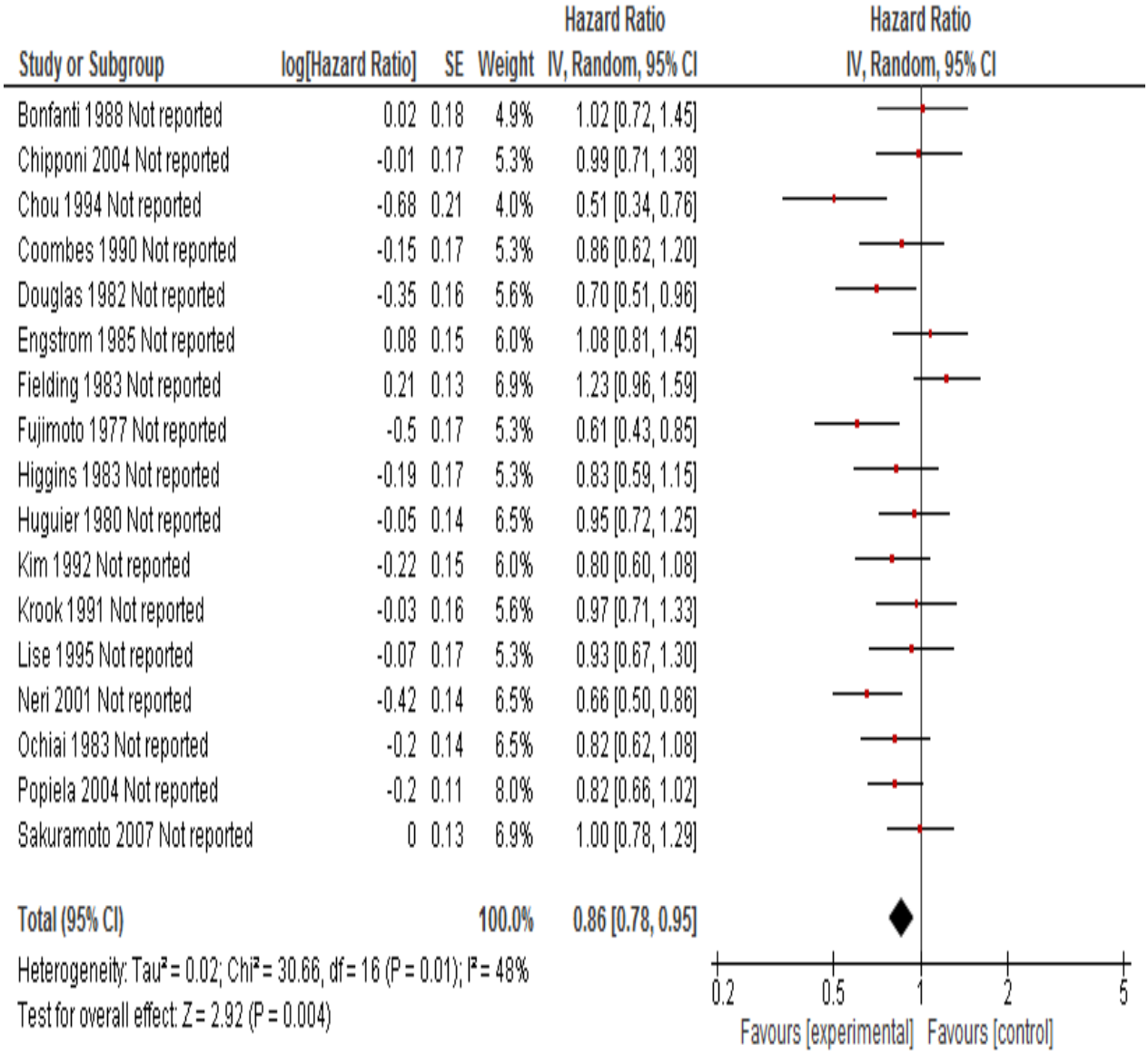


Figure 7.5: Funnel plot of the RCTs included in the meta-analysis by Diaz-Nieto *et al.*[344] that did not report the period of follow-up for the outcome mortality. There was no evidence of significant publication bias in the analysis of the RCTs that did not report the period of follow-up.

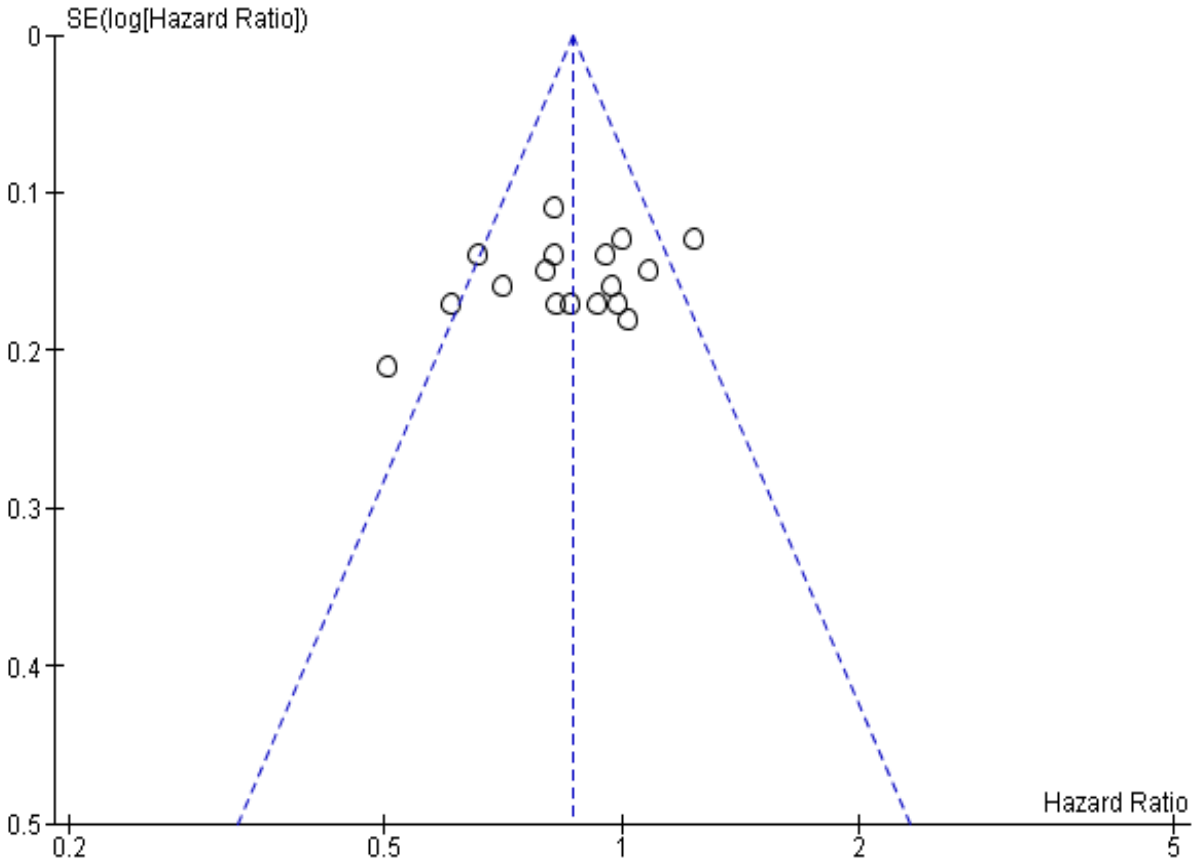


Figure 7.6: Forest plot of the RCTs included in the meta-analysis by Diaz-Nieto *et al.*[344] that reported the period of follow-up for the outcome disease recurrence. This forest plot shows that RCTs on adjuvant chemotherapy for gastric cancer reporting the follow-up period showed a significant benefit to adjuvant chemotherapy regarding disease recurrence.

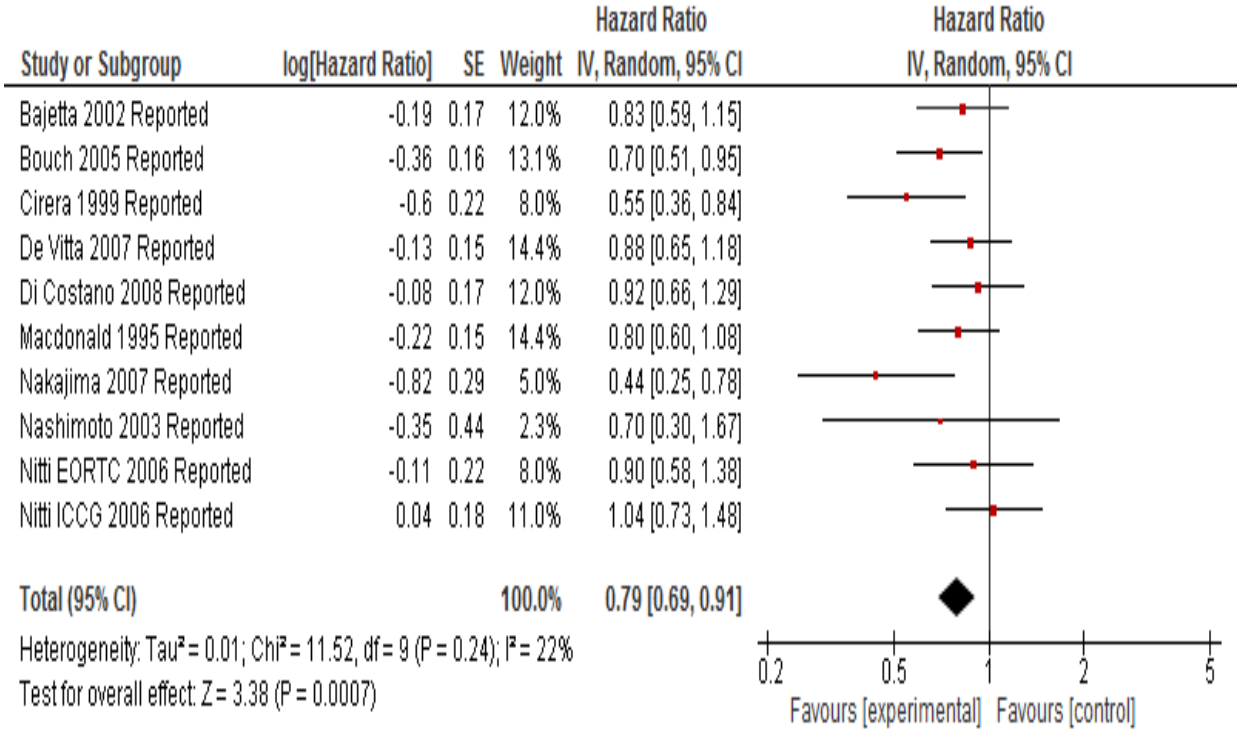


Figure 7.7: Funnel plot of the RCTs included in the meta-analysis by Diaz-Nieto *et al.*[344] that reported the period of follow-up for the outcome disease recurrence. There was no evidence of significant publication bias in the analysis of the RCTs that reported the period of follow-up.

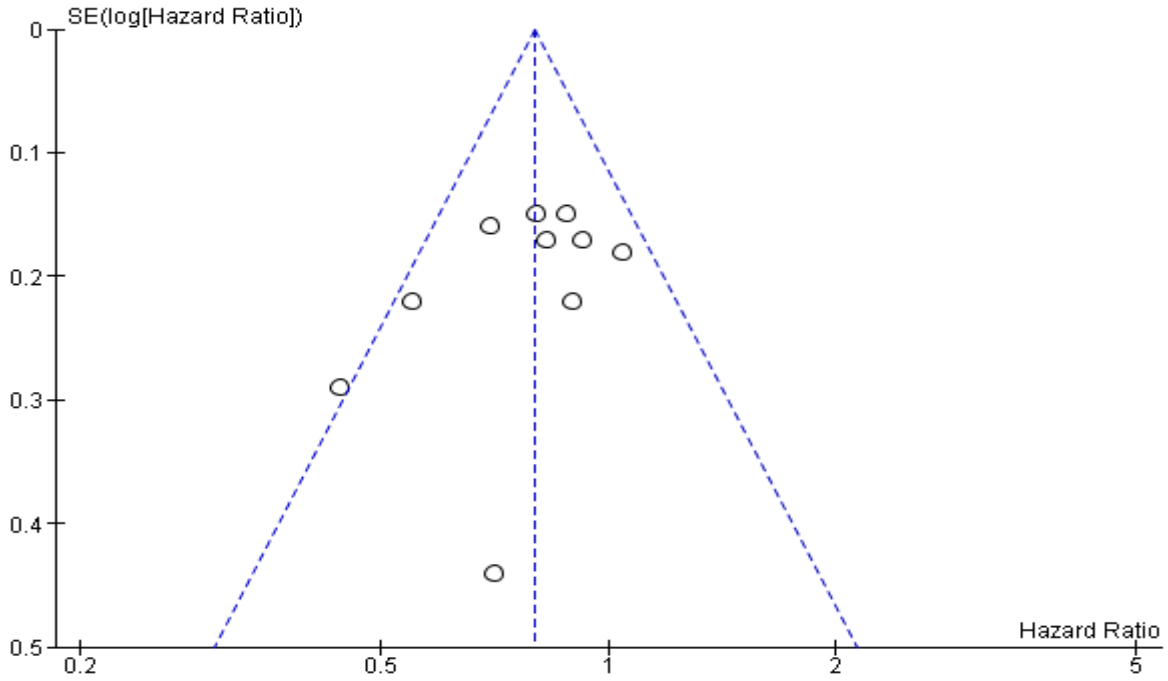


Figure 7.8: Forest plot of the RCTs included in the meta-analysis by Diaz-Nieto *et al.*[344] that did not report the period of follow-up for the outcome disease recurrence. This forest plot shows that RCTs on adjuvant chemotherapy for gastric cancer not reporting the follow-up period showed a significant benefit to adjuvant chemotherapy regarding disease recurrence. These results are similar to Figure 8.6, for the RCTs in the same meta-analysis reporting the follow-up period

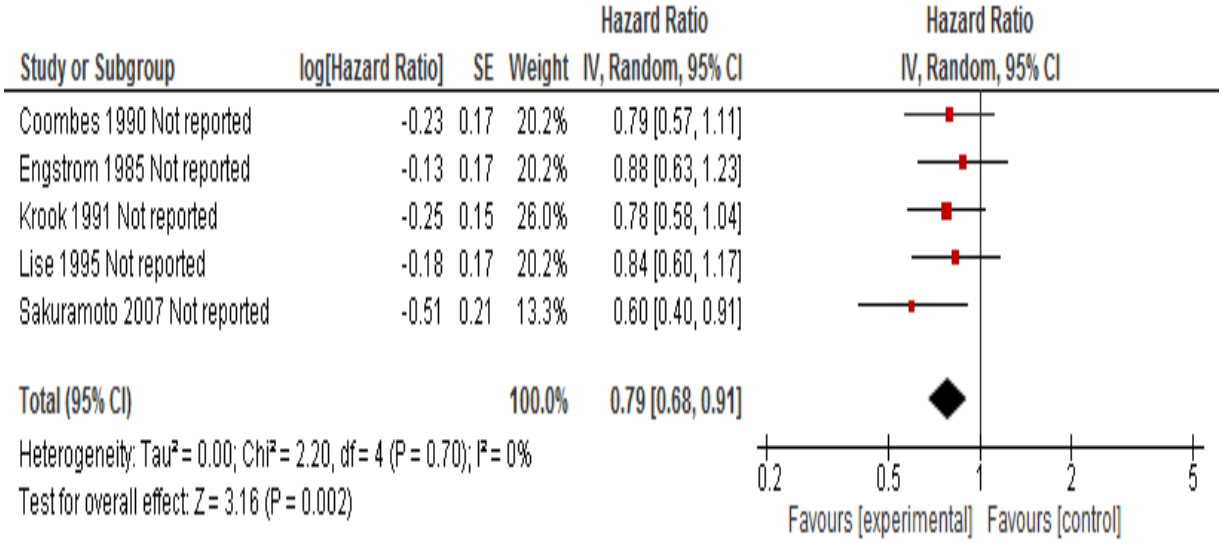
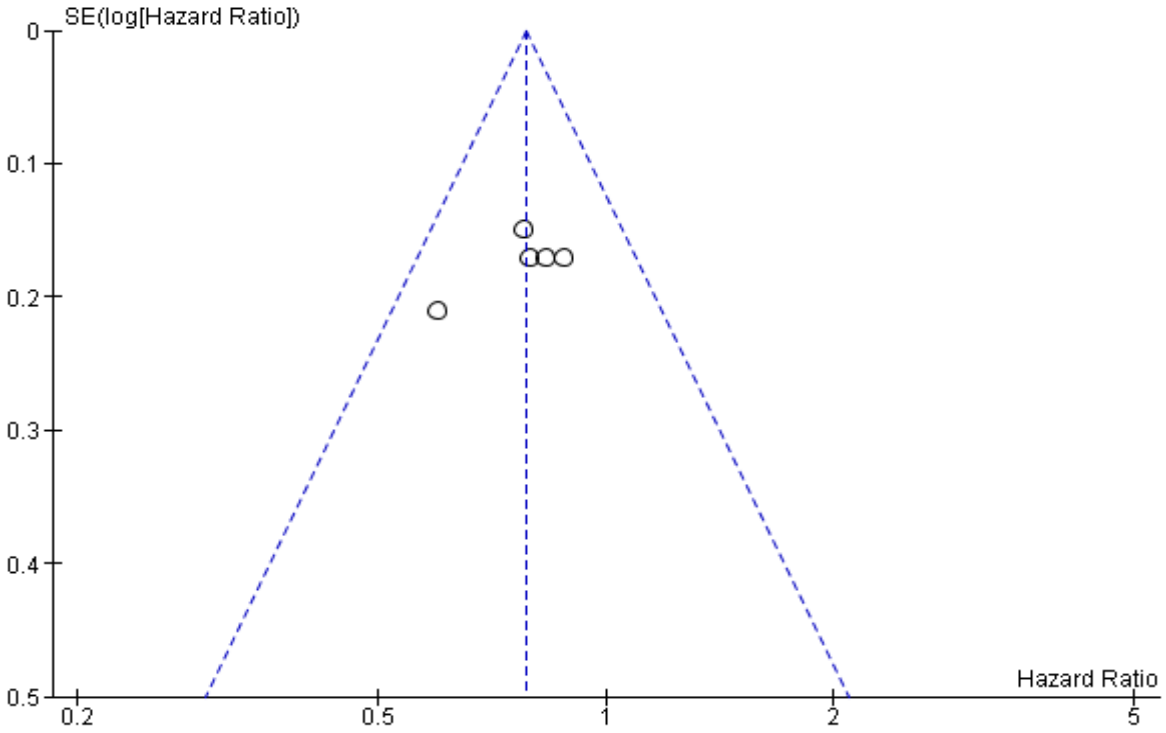


Figure 7.9: Funnel plot of the RCTs included in the meta-analysis by Diaz-Nieto *et al.*[344] that did not report the period of follow-up for the outcome disease recurrence. There was no evidence of significant publication bias in the analysis of the RCTs that did not report the period of follow-up.



The relative HR of the trials in the meta-analysis by Diaz-Nieto *et al.*[344] that reported the follow-up period versus the trials that did not report the period of follow-up for the outcome mortality was calculated to be HR=1, with 95% CI 0.880 to 1.137, with LnHR=0, and SE(LnHR)=0.065. The relative HR of the trials that reported the follow-up period versus the trials that did not report the period of follow-up for the disease recurrence was calculated to be HR=1, with 95% CI 0.818 to 1.223, with LnHR=0, and SE(LnHR)=0.103. Then, these results for the meta-analysis by Diaz-Nieto *et al.*, together with the results of the other included Cochrane meta-analyses, were used in RevMan for the overall analysis.

The overall analysis for the outcome mortality is shown in Figure 7.10, and for the outcome disease recurrence is shown in Figure 7.11. No significant difference in mortality was found between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up (HR 0.98, 95% CI 0.93, 1.03; P=0.43), with no significant heterogeneity between the included meta-analyses (P=0.69; I-square 0%). Also, no significant difference in disease recurrence was identified between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up (HR 0.88, 95% CI 0.77, 1.02; P=0.10), with significant heterogeneity between the meta-analyses (P=0.06; I-square 46%).

Figure 7.10: Overall analysis for the outcome mortality. There was no significant difference in mortality between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up.

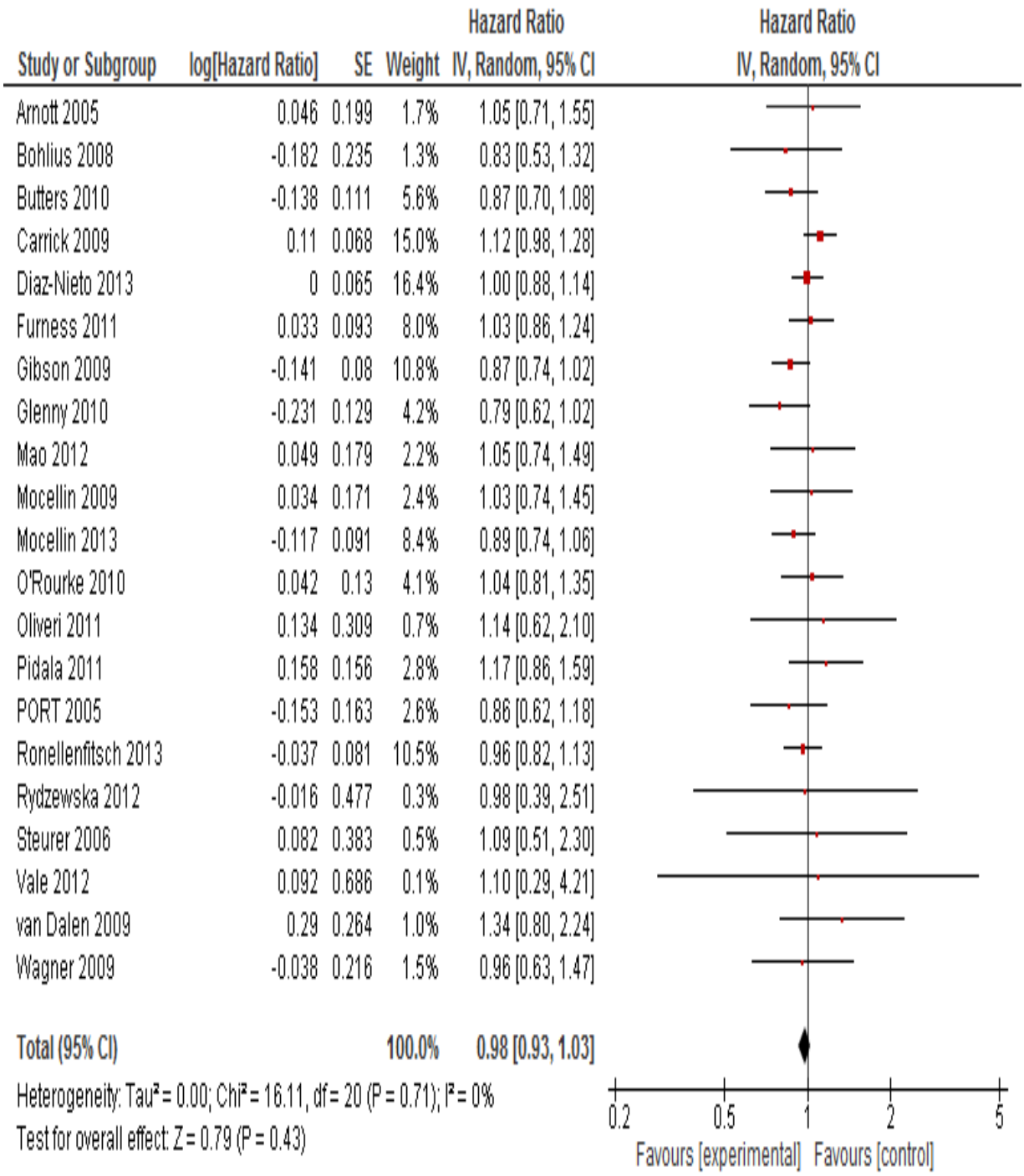
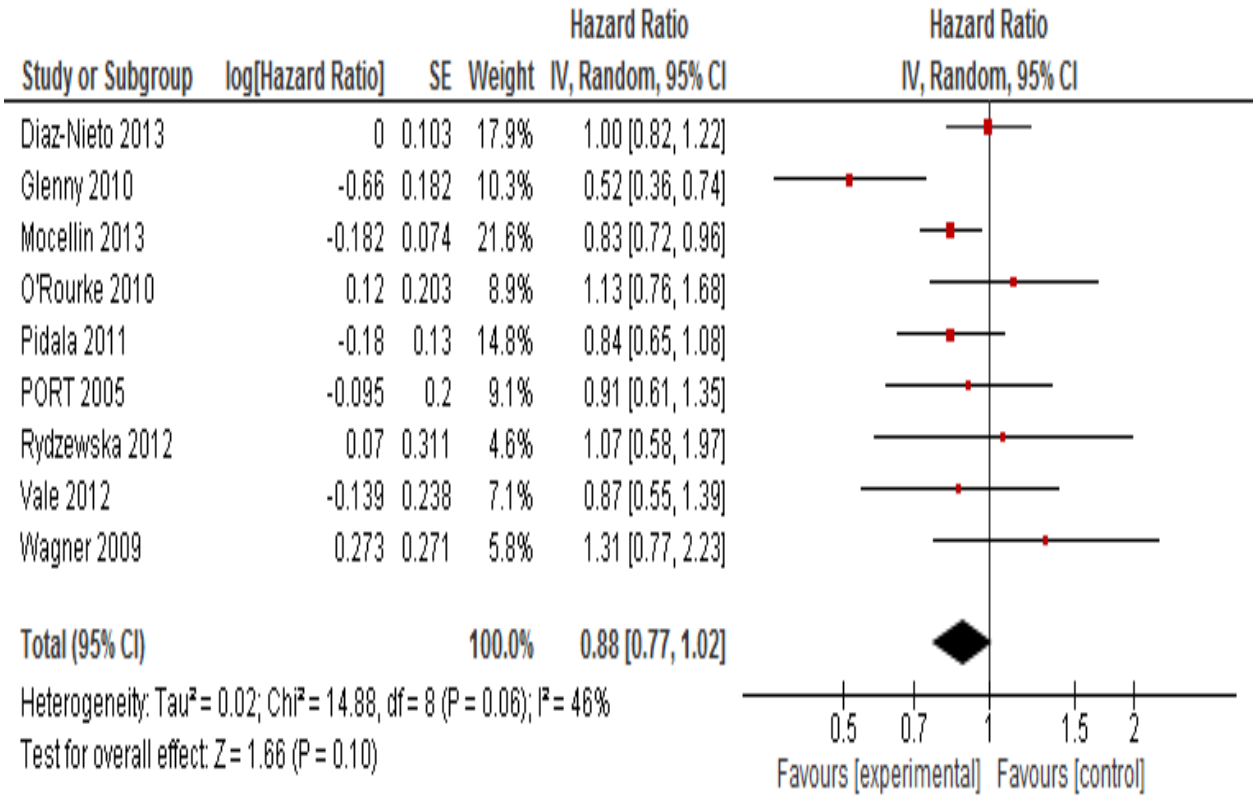


Figure 7.11: Overall analysis for the outcome disease recurrence. There was no significant difference in disease recurrence between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up, with significant heterogeneity between the meta-analyses.



7.3.2 Sensitivity analysis

Sensitivity analysis of more recent Cochrane meta-analyses published after 2010 for the outcome mortality is shown in Figure 7.12, and for the outcome disease recurrence is shown in Figure 7.13. No significant difference in mortality was found between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up (HR 0.99, 95% CI 0.92, 1.07; P=0.81), with no significant heterogeneity between the meta-analyses (P=0.92; I-square 0%). A significant difference in disease recurrence was identified between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up (HR 0.88, 95% CI 0.80, 0.98; P=0.02), with no significant heterogeneity between the meta-analyses (P=0.62; I-square 0%). The trials that reported the period of follow-up were found to have a significantly lower HR for disease recurrence compared to the trials that did not report the period of follow-up.

Figure 7.12: Sensitivity analysis – meta-analyses published after 2010, for the outcome mortality. There was no significant difference in mortality between the trials reporting and not reporting the period of follow-up.

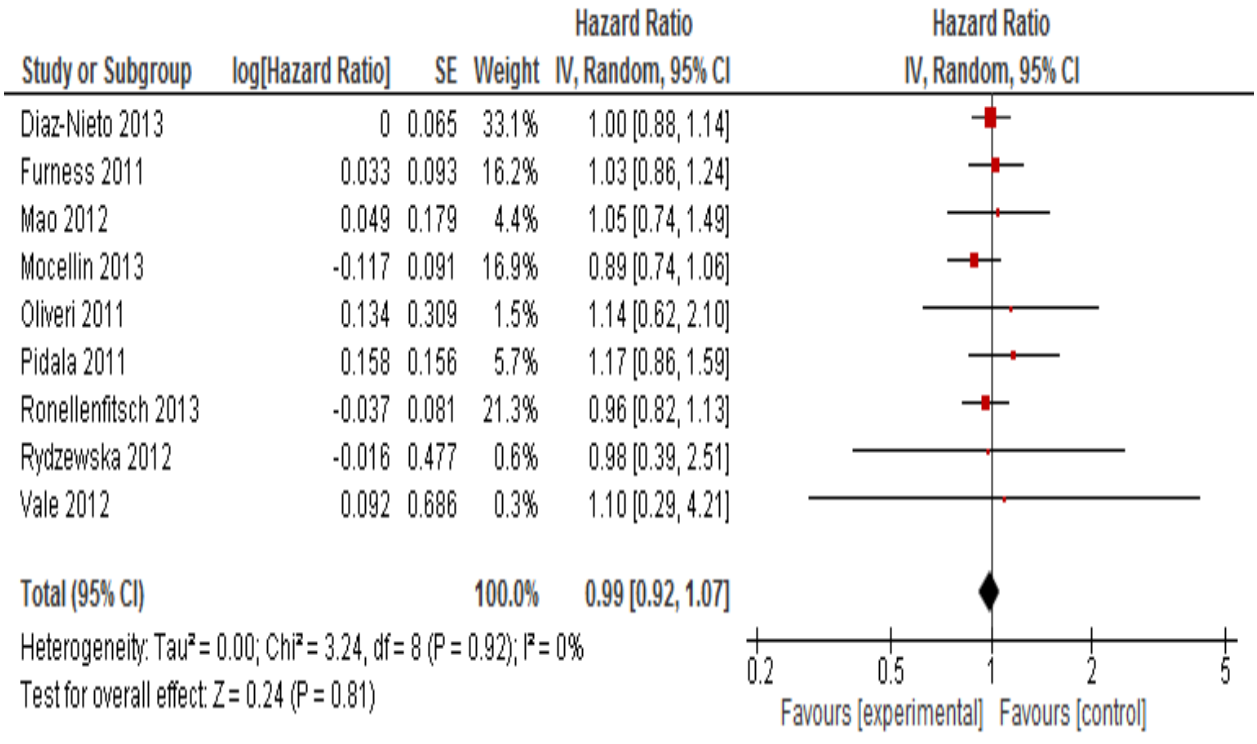
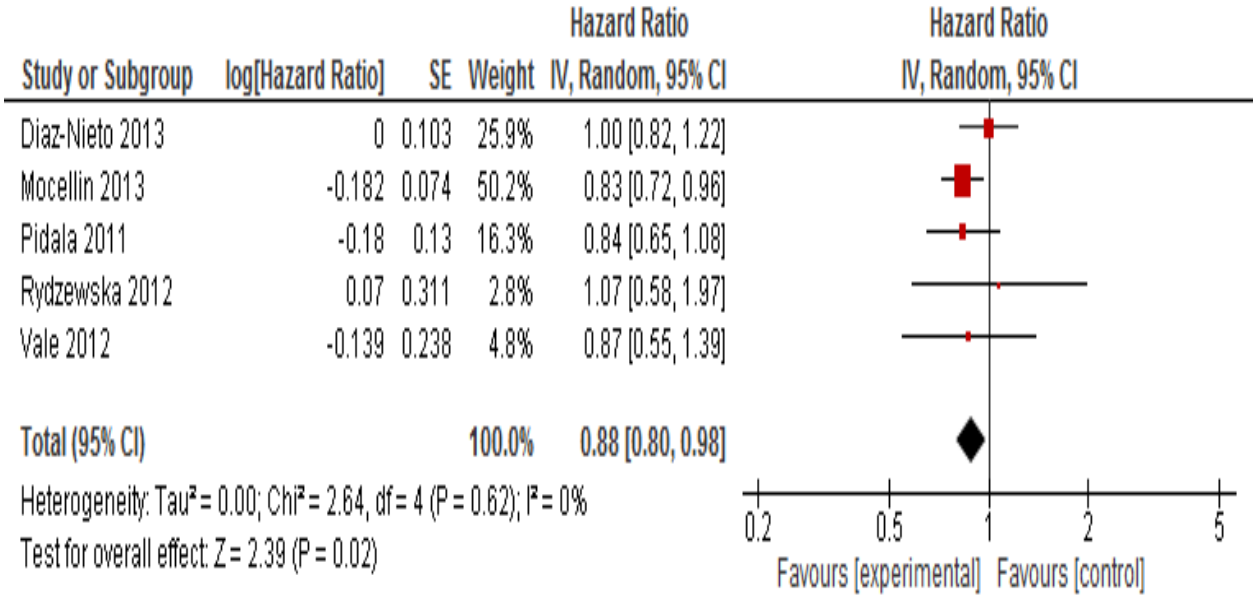


Figure 7.13: Sensitivity analysis – meta-analyses published after 2010, for the outcome disease recurrence. There was a significant difference in disease recurrence between the trials that reported the period of follow-up and the trials that did not report the period of follow-up. The trials that reported the period of follow-up were found to have a significantly lower HR for disease recurrence compared to the trials that did not report the period of follow-up.



Sensitivity analysis of Cochrane meta-analyses including 10 or more RCTs for the outcome mortality is shown in Figure 7.14, and for the outcome disease recurrence is shown in Figure 7.15. No significant difference in mortality was demonstrated between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up (HR 0.97, 95% CI 0.90, 1.03; P=0.32), with no significant heterogeneity between the meta-analyses (P=0.22; I-square 24%). A significant difference in disease recurrence was found between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up (HR 0.81, 95% CI 0.66, 0.99; P=0.04), with significant heterogeneity between the meta-analyses (P=0.02; I-square 70%). The trials that reported the period of follow-up were found to have a significantly lower HR for disease recurrence compared to the trials that did not report the period of follow-up.

Figure 7.14: Sensitivity analysis – meta-analyses including 10 or more trials, for the outcome mortality. There was no significant difference in mortality between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up.

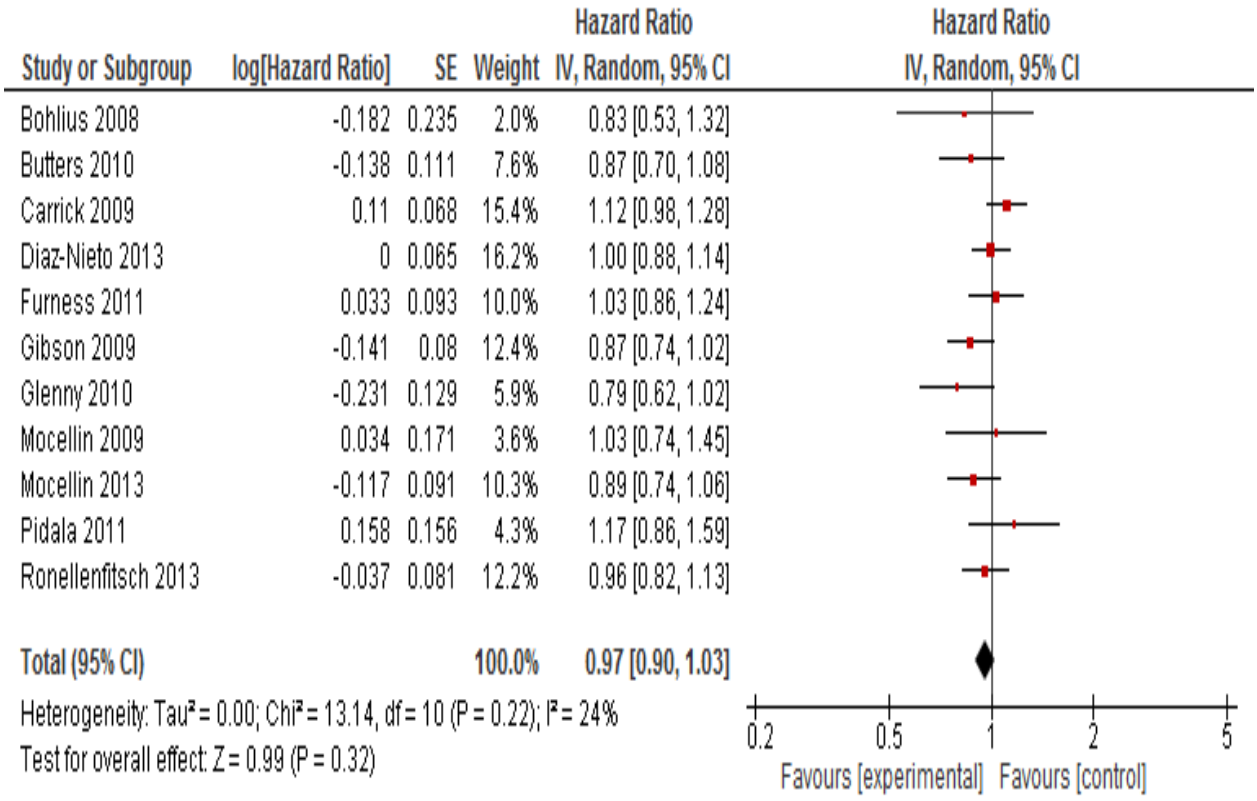
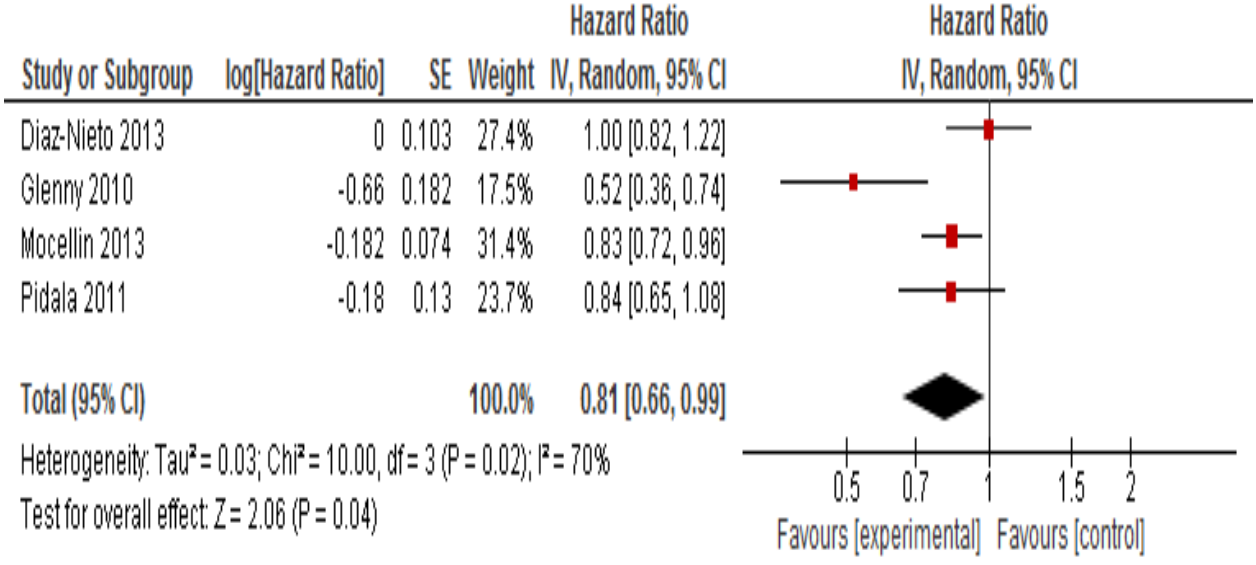


Figure 7.15: Sensitivity analysis – meta-analyses including 10 or more trials, for the outcome disease recurrence. There was a significant difference in disease recurrence between the trials that reported the period of follow-up versus the trials that did not report the period of follow-up, with significant heterogeneity. The trials that reported the period of follow-up were found to have a significantly lower HR for disease recurrence compared to the trials that did not report the period of follow-up.



7.4 DISCUSSION

The period of follow-up of the participants included in trials comparing treatments for cancer or chronic diseases with time to event outcomes may make vital differences to the perceived efficacy of treatment. Especially when comparing treatments for cancer and reporting on survival and/or cancer recurrence, the length of follow-up of the participants is an important factor when assessing the long-term comparative benefits or harms of these treatments. This review was performed to analyse studies reporting on time-to-event outcomes (survival, disease recurrence) and to investigate if not reporting the period of follow-up is a potential source of bias.

Overall, this review did not identify a significant difference in the time-to-event outcomes mortality and disease recurrence between trials that reported the period of follow-up and trials that did not report the period of follow-up. However, there was a trend towards statistical significance for a difference in disease recurrence (P=0.10), with trials reporting the period of follow-up to have a lower HR for disease recurrence compared to the trials that did not report the period of follow-up. Importantly, sensitivity analysis of more recent meta-analyses published after 2010 and larger meta-analyses including 10 or more RCTs identified significant difference for the outcome disease recurrence between trials reporting the period of follow up and trials not reporting the period of follow-up. The trials that reported the period of follow-up were found to have a significantly lower HR for disease recurrence compared to the trials that did not report the period of follow-up. There was no significant heterogeneity for the sensitivity analysis of more recent meta-analyses, but there was significant heterogeneity for the sensitivity analysis of larger meta-analyses for disease recurrence. For the outcome mortality, sensitivity analyses of more recent and larger meta-analyses showed no significant difference between trials reporting and trials not reporting the duration of follow-up.

The findings may have been statistically significant for the outcome disease recurrence and not for mortality, because shorter variations in time of follow-up would affect more significantly the outcome disease recurrence, rather than the outcome mortality. The significant results for disease recurrence may suggest that not reporting the duration of follow-up in a trial comparing treatments for a chronic disease is a possible source of bias. Also, the fact that the trials not reporting the period of follow-up were found to

have a significantly higher HR suggests that these trials may report a higher HR of the intervention versus control more commonly leading to a significant advantage in disease free survival for the control group compared to the intervention treatment group, and possibly leading more commonly to Type II errors (i.e. not identifying a statistically significant difference between the two groups when actually there is a difference). It is expected that a trial looking at long-term outcomes would follow the participants long-enough to assess these outcomes correctly. Reporting the period of follow-up in a trial, allows the reader to confirm that participants were followed-up for an adequate period of time to make the results of the trial valid.

Heterogeneity was identified for disease recurrence during the overall analysis and sensitivity analysis of larger meta-analyses. The most likely cause for heterogeneity is that the Cochrane reviews included in this study were investigating different types of chronic diseases and different types of cancers, and were comparing different types of treatments. Unfortunately, there were no available Cochrane reviews including only RCTs reporting on long-term outcomes of treatments for CLM. Other possible causes of heterogeneity are trial design and methodology, selection criteria for their participants, life expectancy, and rate of recurrence of the chronic diseases investigated by the reviews. To minimise bias, for a Cochrane meta-analysis to be included in this study, the trials included in the Cochrane review were RCTs, at least two of these trials were reporting the period of follow-up, and at least two of the trials were not reporting the period of follow up.

Survival and disease recurrence are the primary outcomes in trials comparing different treatments in patients with cancer. In order to reach the appropriate conclusions, trials comparing treatments for CLM should follow patients long enough to detect differences in survival or cancer recurrence. It is important to remember that the conclusions and suggestions given by trials comparing treatments for CLM, or any other type of cancer, comparing survival and disease recurrence rates, may result in changes in the management of patients suffering and dying from cancer. Therefore, as researchers and clinicians designing trials, it is our duty to minimise any potential sources of bias and attempt to reach valid conclusions from our trials.

There are numerous sources of bias in studies which can result in deviation from the truth, in results and inferences. Bias can vary in both magnitude and direction leading to

underestimation or overestimation of the observed effect in comparative trials.[361] The importance of developing a standardised tool for assessing the risk of bias is reflected by the number of scales and checklists developed to assess the validity of RCTs.[362, 363] Between 2005 and 2007 the Cochrane Collaboration developed a domain-based evaluation for assessing risk of bias.[141] The domains included were sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias.[210-216]. These were the domains used in Chapters 5, 6, and 7 to assess the bias of the included trials. In this review, the attempt was to raise the concern that not reporting the period of follow-up is another source of bias. The observed variability of length of follow-up in comparative trials, and the lack of a standardised time-scale during which unfavourable outcomes such as recurrence of disease and mortality are identified and reported, can act as a potential source of bias in comparative trials.

To answer some of the important controversies in the management of CLM requires prospective clinical trials of the interventions. There are different ways to approach the question of whether different periods of follow-up can affect the results of comparative trials comparing treatments for CLM. One method would be to compare two trials of same treatment with different follow-up periods. Another way to address this problem would be to compare survival analysis in trials with short-term follow-up versus trials with long-term follow-up, e.g. compare outcomes of CLM resection trials with less than 2-year follow-up period versus 5-year follow-up period. A further method would be to compare trials with actuarial survival analysis versus trials with an actual long-term follow-up period.

The optimal follow-up period in comparing treatments in patients with CLM with regards to survival benefit or disease recurrence is not known. While following these patients for a long period will provide definitive answers, a long follow-up period will increase the trial costs and delay the adoption of new treatments, while a short period of follow-up may not be informative. At present, there is no consensus amongst surgeons for the ideal follow-up time period after liver resection for CLM in order to identify recurrence of disease. Cox proportional hazard model is generally used to compare treatments, but it assumes the hazard ratio of death between the intervention and control to be constant over time. This may be untrue in treatments comparing surgery and other interventions (e.g. radiofrequency ablation, chemotherapy) in patients suffering with

CLM. Deaths in the surgery group usually happen due to two reasons: due to the surgery itself and due to the cancer; while the deaths in the other treatments occur mainly due to the cancer. Therefore, a short follow-up period will result in bias against surgery since mortality is higher earlier on in surgery, whereas there is no early mortality in the less invasive treatment. The general belief is however that the patients who survive surgery for resection of cancer are more likely to have achieved cure compared to non-invasive treatments. But this benefit of survival by surgical treatment is unlikely to be seen unless the patients have been followed up for a sufficiently long time for the disease to recur and progress.

Further research is needed to identify the required follow-up time period for patients with CLM to assess overall survival rates and disease free survival rates. One method to determine the optimal follow-up period to assess overall survival rates would be to calculate the overall HR and 95% CI at maximal follow-up (i.e. death of the patients) and different potential periods of follow-up. This will typically involve calculation of HR and 95% CI if every patient was followed for a period of 1 month or until death; if every patient was followed for a period of 2 months or until death, and so on. It is anticipated that the HR will not change beyond a set period of follow-up; similarly, the variance of the HR will not change beyond another set period of follow-up. This set period of follow-up for patients with CLM, would be the optimal period of follow-up, between short-term and long-term follow-up, at which further follow-up of patients is unlikely to alter the effect estimate. Until the required period of follow-up is known, trials comparing treatments for patients suffering with CLM should follow-up the patients for an adequate period of time, and should report this period of time to allow clinicians to critically appraise the results of the trial and to guide researchers into future trial design.

7.5 CONCLUSIONS

To answer some of the important controversies in the management of CLM requires prospective clinical trials of the interventions, with adequate period of follow-up of the participants, to assess survival and disease recurrence. The aim of this review was to analyse studies reporting on time-to-event outcomes (survival, disease recurrence) in the literature and investigate if not reporting the period of follow-up in comparative trials is a potential source of bias. Although, overall analysis did not identify a significant difference in mortality and disease recurrence between trials that reported the period of follow-up and trials that did not report the period of follow-up, sensitivity analysis of more recent reviews and larger reviews showed a significant difference in disease recurrence between trials reporting, and trials not reporting, the period of follow up. The trials that reported the period of follow-up were found to have a significantly lower HR for disease recurrence compared to the trials that did not report the period of follow-up. The lack of follow-up reporting in comparative trials may be considered as a new source of trial bias, and it is expected by trials comparing treatments for patients suffering with CLM to follow-up the patients for an adequate period of time, and to report this time period. Further research is required into identifying the required follow-up time period for patients with CLM to assess overall survival rates and disease free survival rates.

CHAPTER 8

OVERALL DISCUSSION AND FUTURE STUDIES

8.1 OVERALL DISCUSSION AND FUTURE STUDIES

The overall aim of this thesis was to use an evidence based approach to answer some of the important controversies in the surgical management of patients suffering with CLM. There are many unanswered questions in the surgical management of CLM, and CLM is a clinical subject for which there is a vast array of information available in the medical literature. An evidence-based approach allows a researcher or clinician to follow formal, explicit methods to summarise and analyse the available scientific evidence, evaluate and critically appraise the evidence, and attempt to answer important clinical questions to improve the care of patients. These important clinical questions may not have been possible to be answered confidently by individual studies in the literature due to their small individual size or conflicting results.

Meta-analyses have been used in this thesis to help resolve medical controversies or uncertainties in the management of patients with CLM. By pooling all the results of the individual studies, a meta-analysis has more power than individual studies to identify a true difference that exists between treatments, and increases the precision in estimating the size of the effects of difference between treatments. Network meta-analyses have also been used in this thesis, which is a new method of comparison of different treatments, and is ideal when multiple treatments have been used and compared for the same disease and outcomes in different head-to-head comparisons. A network meta-analysis, unlike a standard pairwise meta-analysis, allows comparison of multiple treatments simultaneously, and combines direct evidence within trials and indirect evidence across trials facilitating indirect comparisons of multiple interventions that have not been studied in a head-to-head fashion.

Currently, there is no consensus between surgeons on the optimal timing of liver resection for resectable synchronous CLM. A meta-analysis was performed to compare the short-term and long-terms outcomes in patients with synchronous CLM undergoing combined resection versus sequential resection. The meta-analysis demonstrated that combined resection is associated with reduced hospital stay and with comparable perioperative mortality and morbidity, operative blood loss, blood transfusion requirements, survival rates and recurrence-free rates as sequential resection. The meta-analysis confirmed that in the presence of limited hepatic disease, combined resection is safe and produces the same oncological outcomes as sequential resection for patients

with synchronous CLM. However, the findings of this meta-analysis were limited by significant differences in metastatic disease severity and location of the primary tumour between the combined and sequential resection groups, the retrospective nature of the included studies, and the heterogeneity identified between studies. Therefore, well designed RCTs are required to compare combined versus sequential resection for synchronous CLM with appropriate selection criteria taking into consideration the metastatic burden and the location of the primary tumour. Also, future RCTs should clearly define the strategy used for the colorectal resection and for the liver resection (e.g. laparoscopic or open, or methods used to decrease blood loss), and should follow-up patients for an adequate period of time to assess mortality and disease recurrence rates.

Involvement of hepatic lymph nodes during liver resection is considered as a poor prognostic factor, and liver resection for CLM in the presence of hepatic lymph node involvement is controversial. A meta-analysis was performed to determine the prognostic significance of hepatic lymph node status in patients undergoing hepatectomy for CLM and to determine whether hepatectomy is indicated in patients with nodal involvement. The meta-analysis demonstrated that the survival rates are lower in node positive disease patients compared to node negative disease patients, irrespective of: the extent/location of the lymph node dissection, whether the positive disease nodes were detected by routine or selective lymphadenectomy, whether the nodal involvement was microscopic or macroscopic, and whether adjuvant or neoadjuvant chemotherapy was used. The meta-analysis concluded that there is no evidence of survival benefit from routine lymphadenectomy, and no proven benefit of liver resection with lymphadenectomy for CLM with nodal disease.

The meta-analysis identified a wide variation between studies in the prevalence of disease positive lymph nodes for patients undergoing liver resection for CLM. Further research is required to identify the reasons for this significant variation, for example, patient selection for surgery, the adequacy of pre-operative staging, preoperative and intraoperative assessment, the number of nodes examined, the number of sections per node, special techniques to identify microscopic involvement, and neoadjuvant chemotherapy. Also, there was no data available on the extent of recurrent disease, as it would have been important to know how recurrent disease presents (i.e. more extensive disease, more liver metastases or more extensive lymphatic dissemination) and whether

there would be a difference in recurrent disease between patients who had resection of nodal metastases. Furthermore, chemotherapy regiments have significantly improved over the years for the treatment of CLM and adjuvant or neoadjuvant chemotherapy may play a role in patients undergoing resection where positive lymph nodes have been identified. A selected group of patients who responded to neoadjuvant chemotherapy with resectable CLM combined with hilar nodal involvement could be considered for an RCT offering surgical resection (liver resection and lymphadenectomy) and chemotherapy versus chemotherapy alone.

Liver resection is the only curative option for people with CLM but is a major surgical procedure with significant mortality and morbidity. Operative blood loss and perioperative blood transfusion are two of the most important factors affecting perioperative morbidity and mortality during liver resection. A network meta-analysis was performed to assess the comparative benefits and harms of different treatment strategies aiming to decrease operative blood loss and blood transfusion, by combining the methods of vascular occlusion, parenchymal transection, and management of the cut surface of the liver that a surgeon would typically use during the operation. No differences between treatment strategies were identified in mortality, length of hospital stay or ITU stay. There were more serious adverse events when surgery was performed using radiofrequency dissecting sealer compared with the standard clamp-crush method in the absence of vascular occlusion and fibrin sealant. Liver resection with intermittent vascular occlusion resulted in higher amounts of blood transfusion than liver resection with continuous vascular occlusion when the parenchymal transection was carried out with the clamp-crush method and no fibrin sealant was used for the cut surface. No evidence was found to prefer one treatment strategy over another, but simple methods, such as clamp-crush method, gave equivalent outcomes to other methods which require special equipment.

There was a difficulty in identifying trials which would meet the inclusion criteria for the above mentioned network meta-analysis. Many RCTs which included comparisons of one aspect of different methods of vascular occlusion or parenchymal transection or management of cut surface, had to be excluded because one or more aspects of methods of vascular occlusion or parenchymal transection or management of cut surface not being compared were either not stated or were chosen in a non-random manner. Due to the few trials that could be included for network meta-analysis in this review and the

sparsity of data, the individual interventions included in the treatment strategies had to be revised into fewer categories. This new method of combining interventions aiming to decrease blood loss during liver resection into a treatment strategy can prevent methodology bias in future trials. Future trials are needed to compare treatment strategies aiming to decrease blood loss and blood transfusion and assess patient outcomes after hepatectomy. Such trials should attempt to control other possible confounding factors, for example, cirrhotic or non-cirrhotic livers, major or minor liver resections, periods of occlusion and non-occlusion of intermittent portal triad clamping, maximum periods for continuous vascular occlusion, and use of ischaemic preconditioning.

Many interventions have been used to decrease IR injury during liver resection. CRM remains by far the most common indication for liver resection. A network meta-analysis (in Appendix) was performed to assess the comparative benefits and harms of these interventions. No significant difference was identified between the different interventions in mortality, quantity of blood transfusion, and ITU stay. Although no significant evidence was found to recommend one intervention over another, ischaemic preconditioning showed promising results because it resulted in fewer serious adverse events, lower operative blood loss, fewer transfusion proportions, and shorter operative time compared to other interventions. Ischaemic preconditioning should be used more routinely to benefit patients undergoing liver resection for CLM, but further RCTs are needed to confirm these important findings, in order to allow ischaemic preconditioning to become standard practice during liver resection for CLM.

In addition, a cost effectiveness study should be performed on the use of ischaemic preconditioning during liver resection, and a long-term study is required to examine the effects ischaemic preconditioning may have on the long-term cancer outcomes. Furthermore, sensitivity analysis suggested a decrease in serious adverse events from the use of sevoflurane (a volatile anaesthetic), verapamil (a calcium channel blocker), and gabexate mesilate (a thrombin inhibitor) during liver resection, and further RCTs are required to investigate the possible beneficial effects of these three drugs. This network meta-analysis could be used to design future RCTs related to the treatment of IR injury during liver resection surgery and the impact of treatment on costs, quality of life, and long-term outcomes.

To answer some of the important controversies in the management of CLM requires prospective clinical trials comparing treatments, with adequate period of follow-up of the participants, in order to reach correct conclusions about the long-term comparative benefits or harms of these treatments. Survival and disease recurrence are the main outcomes when comparing treatments for CLM, and long period of follow-up is required to assess these outcomes. During the course of this thesis, it was noted that the period of follow-up was inadequately reported by trials comparing time-to-event outcomes for CLM, raising the concern that not reporting the period of follow-up would introduce significant bias in these trials. A review of the literature was performed to analyse studies reporting on time-to-event outcomes (survival, disease recurrence) and investigate if not reporting the period of follow-up in comparative trials is a potential source of bias. Although overall analysis did not identify a significant difference in mortality and disease recurrence between trials that reported the period of follow-up and trials that did not report the period of follow-up, sensitivity analysis of more recent reviews and larger reviews showed a significant difference in disease recurrence between trials reporting and trials not reporting the period of follow up.

Further studies could be performed to assess if different periods of follow-up affect the time-to-event outcomes of trials comparing treatments for CLM, and one way to address this problem would be to compare survival analysis in trials with short-term follow-up versus trials with long-term follow-up, e.g. compare outcomes of CLM resection trials with less than 2-year follow-up versus 5-year follow-up. It is expected that trials comparing treatments for patients suffering with CLM to follow-up the patients for an adequate period of time, and to report this period of time to allow clinicians to critically appraise the results of the trial and to guide researchers into future trial design. However, the optimal follow-up period in comparing treatments in patients with CLM with regards to survival benefit is not known. While following these patients for a long period will provide definitive answers, a long follow-up period will increase the trial costs and delay the adoption of treatment whereas a short period of follow-up may not be informative and result in bias against surgery due to the higher early mortality postoperatively compared to non-surgical treatments. Therefore, further research is needed to identify the optimal follow-up time period for patients with CLM to assess overall survival rates and disease free survival rates. The optimal follow-up period could be the time period beyond which there is no significant change in the HR and the variance of the HR.

Overall, the studies included in this thesis have met the individual objectives set and have answered some of the important clinical questions raised in the management of patients suffering with CLM. Furthermore, the importance of using optimum follow-up period in trials comparing treatments for patients suffering with CLM has been demonstrated, and the optimal follow-up period can be determined using analysis of existing databases such as those maintained by cancer networks in the UK. There have been difficulties in giving some answers and these were identified and discussed. In addition, new clinical questions have been raised aiming to promote further research. The patient should be the main focus of any clinical research performed and this thesis is likely to help in the improvement of care for patients suffering with CLM and improvement in design of trials evaluating the management of patients with CLM.

APPENDIX

EFFECTIVENESS AND CLINICAL OUTCOMES OF INTERVENTIONS AIMING TO DECREASE HEPATIC ISCHAEMIA-REPERFUSION INJURY – A NETWORK META-ANALYSIS

A.1 INTRODUCTION

Over the years, indications for liver resection have been broadened and the number of liver resections performed has increased. The number of liver resections performed in the UK has more than doubled over the last 10 years, from around 1000 in 2003 to around 2400 in 2013.[61, 62] The most common reason for liver resection is the resection of colorectal liver metastases (CLM). Other common reasons are HCC, cholangiocarcinoma, and benign liver tumours.[45, 46] Liver resection is a major surgical procedure with significant mortality of around 4% and morbidity of around 40%.[45, 46, 63]

As discussed in Chapter 6, intraoperative haemorrhage remains one of the major risks during liver resections, and operative blood loss and perioperative blood transfusion are two of the most important factors associated with higher perioperative morbidity and mortality.[45, 46, 64, 65] Therefore, minimizing blood loss is of major importance, and methods of hepatic vascular occlusion have been developed over the years to reduce the bleeding during elective liver resection.[66] Clamping of the portal pedicle (Pringle manoeuver, i.e. clamping the hepatic artery and portal vein) is the oldest and commonest method of hepatic vascular occlusion and can be performed either continuously or intermittently during the parenchymal resection.[67-69] Nuzzo et al. compared liver resections with or without hepatic pedicle clamping and found significantly fewer people requiring blood transfusion and significantly lower number of blood units transfused per patient when hepatectomy was performed with hepatic pedicle clamping.[235] A meta-analysis of trials comparing hepatic vascular occlusion versus no vascular occlusion demonstrated no difference in mortality, liver failure, or other morbidities.[66] The blood loss was significantly lower in vascular occlusion compared with no vascular occlusion, but the liver enzymes were significantly elevated in the vascular occlusion group compared with no vascular occlusion.[66] Furthermore, as shown in Chapter 6, liver resection under continuous vascular occlusion with clamp-crush and no fibrin, results in lower operative blood loss and lower blood transfusion requirements.

However, hepatic vascular occlusion, along with mobilization and retraction of the liver during surgery, causes ischaemia and reperfusion (IR) injury to the future liver remnant (FLR). IR injury is more applicable to liver transplantation than liver resection, as majority of liver resection for CLM can be achieved without major vascular clamping,

and the part of the liver concerned intraoperatively from IR injury is resected/removed. Nonetheless, CLM remains by far the most common indication for liver resection. In cases of extensive liver resection where the FLR is small and in cases when the liver suffers from chronic diseases, such as cirrhosis, IR injury can greatly increase the risk of post-operative liver failure resulting in significant increase in postoperative mortality and morbidity.[73, 74, 76, 77] Patients with cirrhotic liver and hepatic steatosis are more sensitive to IR injury than patients with normal liver.[76, 77]

IR injury of the liver involves a number of mechanisms. Ischaemia followed by reperfusion results in the activation of Kupffer cells (liver macrophages) and polymorphonucleocytes, production of reactive oxygen species and pro-inflammatory cytokines, and induction of endothelial cell surface adhesion molecules, resulting in microvascular hypo-perfusion and liver parenchymal damage.[72-74, 364]

Many interventions have been used to decrease IR injury associated with prolonged duration of vascular occlusion with the intention of decreasing perioperative mortality and morbidity.[72] These interventions include hypothermia,[78] mechanical interventions such as ischaemic preconditioning (the mechanism by which brief periods of hepatic vascular occlusion followed by reperfusion results in the ability of the liver to withstand a subsequent prolonged period of ischaemia),[67, 68, 76, 79, 80] ischaemic post-conditioning (a prolonged period of ischaemia during liver resection is followed by brief periods of hepatic ischaemia and reperfusion),[81] and pharmacological interventions such as anti-oxidants,[82] prostaglandins,[83] steroids,[84, 85] different anaesthetic agents,[86, 87] treatments to increase hepatocellular glycogen,[88, 89] and treatments affecting the cardiovascular system.[90, 91] These interventions can be used alone or in combination.

Hypothermia during liver resection reduces the metabolic rate and slows the degeneration of cellular components due to IR injury.[78] The interventions aiming to increase hepatic glycogen are thought to reduce postoperative liver dysfunction by achieving better perioperative glucose control, by preserving liver glycogen stores which may protect hepatocytes, and possibly through an antiapoptotic effect.[88, 365] The anti-inflammatory and immune modulating effects of steroids through cytokine release modulation are thought to be the mechanisms through which steroids may decrease surgical stress and IR injury.[84, 85, 366, 367]

Each individual category of interventions has been systematically reviewed independently previously,[71, 364, 368] and no individual therapy is considered a current standard practice. One pairwise meta-analysis included five RCTs and compared one pharmacological agent versus another pharmacological agent (a total of 9 different pharmacological agents).[71] A statistical meta-analysis of the data with forest plots could not be performed since indirect comparisons of the different pharmacological agents were not possible with a pairwise meta-analysis.[71] Another meta-analysis included fifteen RCTs comparing any pharmacological agent versus placebo or no pharmacological agent.[364] Similar to the previous meta-analysis, indirect comparisons between groups could not be performed, and the only statistical meta-analysis performed was of four RCTs comparing Prostaglandin E1 versus placebo and a meta-analysis of three studies comparing Methylprednisolone versus control.[364] This deficiency of pairwise meta-analyses (to allow only pairwise direct comparisons) has been addressed by the current network meta-analysis.

There has been no previous network meta-analysis comparing different techniques aimed at decreasing IR injury during elective liver resection. A network meta-analysis is ideal for this topic, where multiple interventions have been used and compared for the same disease and outcomes in different head-to-head comparisons. Network meta-analysis combines direct evidence within trials and indirect evidence across trials.[132] Therefore, it allows comparison of interventions that may or may not have been evaluated directly against each other, and allows the relative effectiveness of different treatments to be assessed even if they have not been compared directly in individual RCTs. Furthermore, with a network meta-analysis we can visualize and interpret a wide picture of the evidence and calculate treatment rankings with probabilities.

A.1.1. Aims of this review

The aim of this network meta-analysis is to identify the best methods to decrease IR injury during elective liver resection and to compare the benefits and harms of different interventions aimed at decreasing IR injury.

A.2 METHODS

A.2.1. Search strategy

A comprehensive literature search using a combination of free-text terms and controlled vocabulary when applicable was performed of the following databases: MEDLINE, EMBASE, Science Citation Index Expanded, CENTRAL in The Cochrane Library, and World Health Organization International Clinical Trials Registry Platform. Detailed search strategy is provided in Table A.1. The “related articles” function from PubMed was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed. The references of the identified trials were also searched to identify additional trials for inclusion. No restrictions were made based on language, publication year, or publication status. The latest date for this search was October 6, 2013.

Table A.1: Detailed search strategy.

Database	Time span	Search strategy
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Wiley)	October 6th 2013	#1 (ischaemia OR ischaemia OR ischaemic OR ischaemic OR reperfusion) AND (injury OR injuries OR damage OR damages) #2 MeSH descriptor Reperfusion Injury explode all trees #3 (#1 OR #2) #4 liver OR hepatic OR hepato* #5 MeSH descriptor Liver explode all trees #6 (#4 OR #5) #7 resection OR resections OR segmentectomy OR segmentectomies #8 (#6 AND #7) #9 hepatectomy OR hepatectomies #10 MeSH descriptor Hepatectomy explode all trees #11 (#8 OR #9 OR #10) #12 (#3 AND #11)
MEDLINE (Pubmed)	January 1947 to October 2013	(((ischaemia OR ischaemia OR ischaemic OR ischaemic OR reperfusion) AND (injury OR injuries OR damage OR damages)) OR "Reperfusion Injury"[Mesh])) AND (((liver OR hepatic OR hepato* OR "liver"[MeSH]) AND (resection OR resections OR segmentectomy OR segmentectomies)) OR hepatectomy OR hepatectomies OR "hepatectomy"[MeSH]) AND ((randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
EMBASE (OvidSP)	Janurary 1974 to October 2013	1 (ischaemia or ischaemia or ischaemic or ischaemic or reperfusion).af. 2 (injury or injuries or damage or damages).af. 3 1 and 2 4 exp Reperfusion Injury/ 5 3 or 4 6 (liver or hepatic or hepato*).af. 7 (resection or resections or segmentectomy or segmentectomies).af. 8 6 and 7 9 (hepatectomy or hepatectomies).af. 10 exp Liver Resection/ 11 8 or 9 or 10 12 5 and 11 13 exp crossover-procedure/ or exp double-blind procedure/ or exp randomised controlled trial/ or single-blind procedure/ 14 (random* OR factorial* OR crossover* OR cross over* OR cross-over* OR placebo* OR double* adj blind* OR single* adj blind* OR assign* OR allocat* OR volunteer*).af. 15 13 OR 14 16 12 AND 15
Science Citation Index Expanded	January	#1 TS=((ischaemia OR ischaemia OR ischaemic OR

(http://www.webofknowledge.com/?DestApp=WOS)	1945 to October 2013	ischaemic OR reperfusion) AND (injury OR injuries OR damage OR damages)) #2 TS=((liver OR hepatic OR hepato*) AND (resection OR resections OR segmentectomy OR segmentectomies) OR hepatectomy OR hepatectomies) #3 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #4 #1 AND #2 AND #3
World Health Organization International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/Default.aspx)	October 2013	liver resection OR hepatectomy

A.2.2. Inclusion and exclusion criteria

Only RCTs were considered for this network meta-analysis. Studies of other design were excluded because of the risk of bias in such trials and because it is not appropriate to perform network meta-analysis on studies of different study designs as this will make the interpretation more difficult.[132, 148] The patients included in the analysis underwent elective liver resection, with or without vascular occlusion, and irrespective of the number of segments removed or the nature of the background liver, i.e. normal or cirrhotic liver. RCTs that assessed one or more of the following interventions were included in this review: hypothermia, ischaemic preconditioning, ischaemic postconditioning, and pharmacological interventions. The following comparisons were included: RCTs comparing one of the interventions in the above list with surgery alone, and RCTs comparing one of the interventions in the above list with another intervention in the above list.

A.2.3. Outcomes of interest

The comparative effectiveness of different interventions aimed to decrease liver IR injury during elective liver resection, was assessed for the following outcomes.

Primary outcomes:

- Mortality, evaluated both as short term (30-day mortality or in-hospital mortality) and long term (at maximal follow-up).
- Serious adverse events, defined as any event that would increase mortality, is life-threatening, requires inpatient hospitalization, results in a single organ or multi-organ dysfunction, or requires surgical, endoscopic or radiological intervention to treat it. Serious adverse events correspond to Grade III or above of the Clavien-Dindo classification and in cases where the authors did not classify the severity of adverse events this classification was followed.[250, 251]
- Quality of life.

Secondary outcomes:

- Blood transfusion requirements (proportion of patients requiring red cell or whole blood heterologous blood transfusion, proportion of patients with major blood loss, and mean quantity of units of blood transfusion).
- Operative blood loss in millilitres (mL).
- Operative time in minutes (min).
- Length of hospital stay in days.
- Length of ITU stay in days.
- Time needed to return to work in days.

A.2.4. Data collection

The trials for inclusion were independently identified by two review authors (Constantinos Simillis and Thalia Afxentiou) by screening the titles and abstracts. Full text was sought for any references which were identified for potential inclusion by at least one of the authors, and made further selection for inclusion based on the full text. The following data were independently extracted by two review authors (Constantinos

Simillis and Francis Robertson) from each study: first author, year of publication, language of publication, country, year(s) of conduct of the trial, inclusion and exclusion criteria, sample size, participant characteristics (such as age, sex, underlying disease, comorbidity, number of participants with liver cirrhosis, number of participants with liver steatosis, number of participants undergoing major versus minor liver resection), study design including details of the intervention aimed at decreasing IR injury, outcomes described above, risk of bias. Any discrepancies were resolved through discussion, and if there was still a disagreement between authors, the final decision was taken by a more senior co-author.

The risk of bias of the included trials was assessed based on the following bias risk domains: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and vested interest bias. These bias risk domains were chosen based on the advice of The Cochrane Collaboration,[141] the Cochrane Hepato-Biliary Group Module,[209] and reviews published on network meta-analyses.[132] For further details on the individual bias risk domains please review section 5.2.4. For each of these risk domains of bias the studies were categorized as low risk, uncertain risk, and high risk of bias. A trial was considered at low risk of bias if the trial was assessed as at low risk of bias for all domains. Trials with uncertain risk of bias or with high risk of bias for one or more domains were considered trials with high risk of bias.

A.2.5. Statistical analysis

For detailed description of the statistical methods used to perform the network meta-analysis please review section 3.2.1. For binary outcomes (mortality, serious adverse events, total adverse events, patients requiring blood transfusion), the OR was calculated. For continuous outcomes (quantity of blood transfused, operative blood loss, hospital stay, ITU stay, operating time), the MD was calculated. For each outcome of interest, Stata/IC 11 (StataCorp LP) was used to draw a network plot of all the interventions assessed for that specific outcome Any interventions that were not connected to the other interventions through the network plot were excluded from the analysis of that outcome.

A Bayesian network meta-analysis was conducted using the Markov chain Monte Carlo method in WinBUGS 1.4. The treatment contrast (OR for binary outcomes, MD for continuous outcomes) for any two interventions was modelled as a function of comparisons between each individual intervention and an arbitrarily selected reference group.[152] The reference group in this network meta-analysis was selected to be the surgery alone group. The network analysis was performed as per the guidance from the NICE DSU documents.[153]

The treatment contrasts (OR for binary outcomes and MD for continuous outcomes) of the different treatments in relation to the reference treatment, the deviance residuals, number of effective parameters, and DIC for fixed-effect model and random-effects model were reported for each outcome. Also, the parameters used to assess the model fit (i.e. deviance residuals, number of effective parameters, and DIC) for the inconsistency model were reported. The 95% credible intervals (CrI, similar to 95% confidence intervals in a frequentist method of meta-analysis) were calculated, and the effect estimates and associated 95% CrI for each pairwise comparison were reported in a table.

The probability that a treatment ranks as the best treatment for each outcome of interest, was presented in graphs. The cumulative probability of the treatment ranks (i.e. the probability that the treatment is within the top two, the probability that the treatment is within the top three, etc.) was also presented in graphs. In addition, the probability that each treatment is best for each of the different outcomes (rankogram) was plotted, which is generally considered more informative.[158, 159] The residual deviance and DIC were used for assessing between study heterogeneity as per the guidance from the NICE DSU Technical Support Documents.[153, 154] The between trial SD was also calculated and reported if the random-effects model was used.

An overall network meta-analysis was performed to compare eight classes of active interventions aimed at decreasing IR injury along with a control group which was surgery alone. The classes of intervention were grouped based on their mechanism of action. A sensitivity network meta-analysis was performed to compare all the individual interventions included in each class of intervention aimed at decreasing IR injury. Another sensitivity network meta-analysis was performed to compare the following 4 larger groups: surgery alone, hypothermia, ischaemic preconditioning, and all pharmacological interventions. A third sensitivity network meta-analysis was performed

comparing only the pharmacological interventions aiming to decrease IR injury. Finally, a metaregression was performed based on the percentage of cirrhotic livers included in each trial, and a metaregression based on the percentage of major liver resections performed in each trial.

A.3 RESULTS

A.3.1. Eligible studies

A total of 522 references were identified through electronic searches of CENTRAL (n=60), MEDLINE (n=154), EMBASE (n=119), and Science Citation Index Expanded (n=189). Two hundred and thirty-two duplicates between databases were excluded. A further 220 clearly irrelevant references were excluded through screening titles and reading abstracts. Seventy references were retrieved for further assessment. Five more references were identified for further assessment through scanning reference lists of the identified RCTs. Thirty one references were excluded after reviewing the studies in detail, and in total, 44 RCTs met the inclusion criteria.[67, 68, 76, 78-80, 82-91, 258, 317, 365-367, 369-391] This is summarised in the study flow diagram Figure A.1.

A total of 2457 patients undergoing liver resection were included in the analysis. The included trials with the treatments compared, total number of patients in each trial, and the number with percentages of cirrhotic livers and major liver resections that took place in each trial, are shown in Table A.2. Major hepatectomy was defined as a right or left hemihepatectomy (or lobectomy), or extended hemihepatectomy (or extended lobectomy), or resection of three or more liver segments according to Couinaud.[392] All trials were at high risk of bias according to the criteria set in this analysis. The risk of bias in the included trials is summarised in Figure A.2 and Figure A.3.

Figure A.1: Study flow diagram.

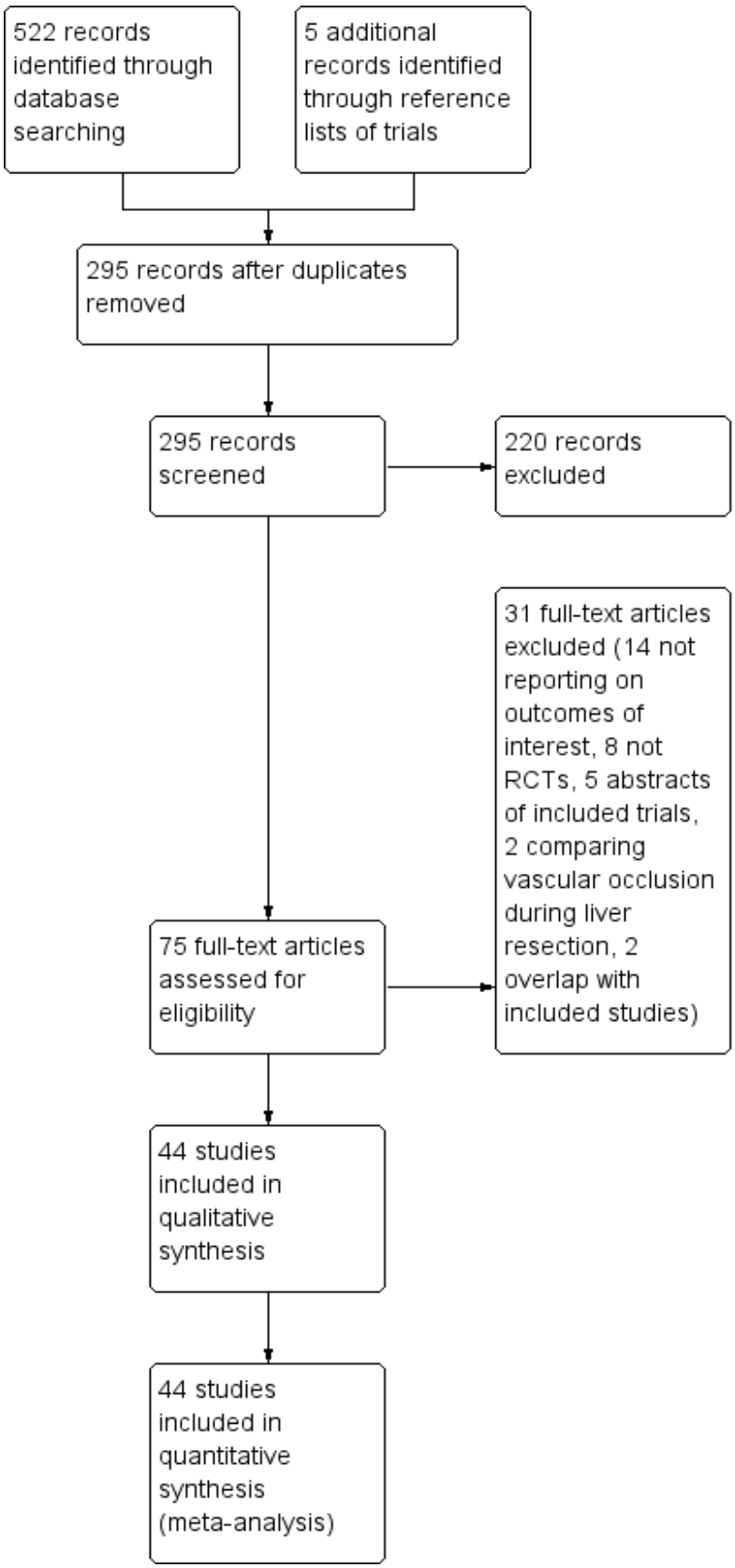


Table A.2: Summary of studies included, showing treatments compared, total number of patients in each study, and the number with percentages of cirrhotic livers and major resections (NR=not reported).

Study	Treatments compared	Total N	Cirrhotic n (%)	Major resections	Study	Treatments compared	Total N	Cirrhotic n (%)	Major resections
Aldrighetti 2006	steroids vs no steroids	73	26 (36)	53 (73)	Li 2004b	ulinastatin vs no ulinastatin	31	27 (87)	NR
Arkadopoulos 2009	ischaemic preconditioning vs no ischaemic preconditioning	84	0 (0)	84 (100)	Liang 2002	ischaemic preconditioning vs no ischaemic preconditioning	29	25 (86)	NR
Azoulay 2006	ischaemic preconditioning vs no ischaemic preconditioning	60	1 (2)	60 (100)	Luo 2009	pre-storing glycogen vs no pre-storing glycogen	38	19 (50)	NR
Bartels 2004	vitamin E vs placebo	47	0 (0)	33 (70)	Marx 2000	dopexamine vs dopamine	19	NR	19 (100)
Beck-Schimmer 2008	sevoflurane vs no sevoflurane	64	0 (0)	28 (44)	Muratore 2003	steroids vs no steroids	53	16 (30)	28 (53)
Beck-Shimmer 2012	sevoflurane vs no sevoflurane	65	0 (0)	26 (40)	Nickkholgh 2011	melatonin vs placebo	36	0 (0)	36 (100)
Cerwenka 1999	antioxidant multivitamin vs no antioxidant multivitamin	50	13 (26)	NR	Nuzzo 2004	ischaemic preconditioning vs no ischaemic preconditioning	42	0 (0)	14 (33)
Chouker 2004	ischaemic preconditioning vs no ischaemic preconditioning	33	0 (0)	9 (27)	Orii 2000	amrinone vs placebo vs prostaglandin E1	45	45 (100)	0 (0)
Clavien 2003	ischaemic preconditioning vs no ischaemic preconditioning	100	0 (0)	75 (75)	Petrowsky 2006	ischaemic preconditioning vs no ischaemic preconditioning	73	0 (0)	44 (60)
Hahn 2011	ischaemic preconditioning vs no ischaemic preconditioning	160	60 (38)	117 (73)	Petrowsky 2010	pentoxifylline vs placebo	101	0 (0)	95 (94)
Hassanain 2013	insulin vs no insulin	56	NR	17 (30)	Scatton 2011	ischaemic preconditioning vs no ischaemic preconditioning	84	0 (0)	78 (93)
Hayashi 2011	steroids vs no steroids	200	NR	26 (13)	Settaf 2001	trimetazidine vs placebo	76	NR	NR
Heizmann 2008	ischaemic preconditioning vs no ischaemic preconditioning	61	0 (0)	19 (31)	Shirabe 1996	OKY046 vs no OKY 046	17	NR	9 (53)
Hou 2009	ischaemic preconditioning vs no ischaemic preconditioning	48	24 (50)	16 (33)	Smyrniotis 2006	ischaemic preconditioning vs no ischaemic preconditioning	54	0 (0)	27 (50)
Ishikawa 2010	branched chain amino acids vs no branched chain amino acids	24	10 (42)	5 (21)	Su 2013	S-adenosyl-L-methionine vs no S-adenosyl-L-methionine	79	79 (100)	33 (42)

Table A.2 continued

Kawano 2005	prostaglandin E1 vs no prostaglandin E1	22	NR	NR	Sugawara 1998	prostaglandin E1 vs placebo	24	24 (100)	0 (0)
Kim 1996	hypothermia vs no hypothermia	20	NR	18 (90)	Tang 2007	hepatocellular glycogen vs no hepatocellular glycogen	57	50 (88)	38 (67)
Kim 2002	gabexate mesilate vs no gabexate mesilate	66	31 (47)	27 (41)	Tsujii 2012	sivelestat vs placebo	50	NR	NR
Kim 2006	gabexate mesilate vs no gabexate mesilate	60	40 (67)	51 (75)	Vriens 2002	allopurinol vs no allopurinol	16	0 (0)	NR
Kostopanagiotou 2006	mannitol vs placebo	30	NR	28 (93)	Winbladh 2012	ischaemic preconditioning vs no ischaemic preconditioning	32	NR	16 (50)
Laviolle 2012	propofol vs desflurane	30	0 (0)	22 (73)	Xia 2009	verapamil vs no verapamil	86	86 (100)	51 (59)
Li 2004a	ischaemic preconditioning vs no ischaemic preconditioning	29	29 (100)	4 (14)	Yamashita 2001	steroids vs no steroids	33	0 (0)	11 (33)

Figure A.2: Risk of bias summary - review authors' judgments about each risk of bias item for each included study.

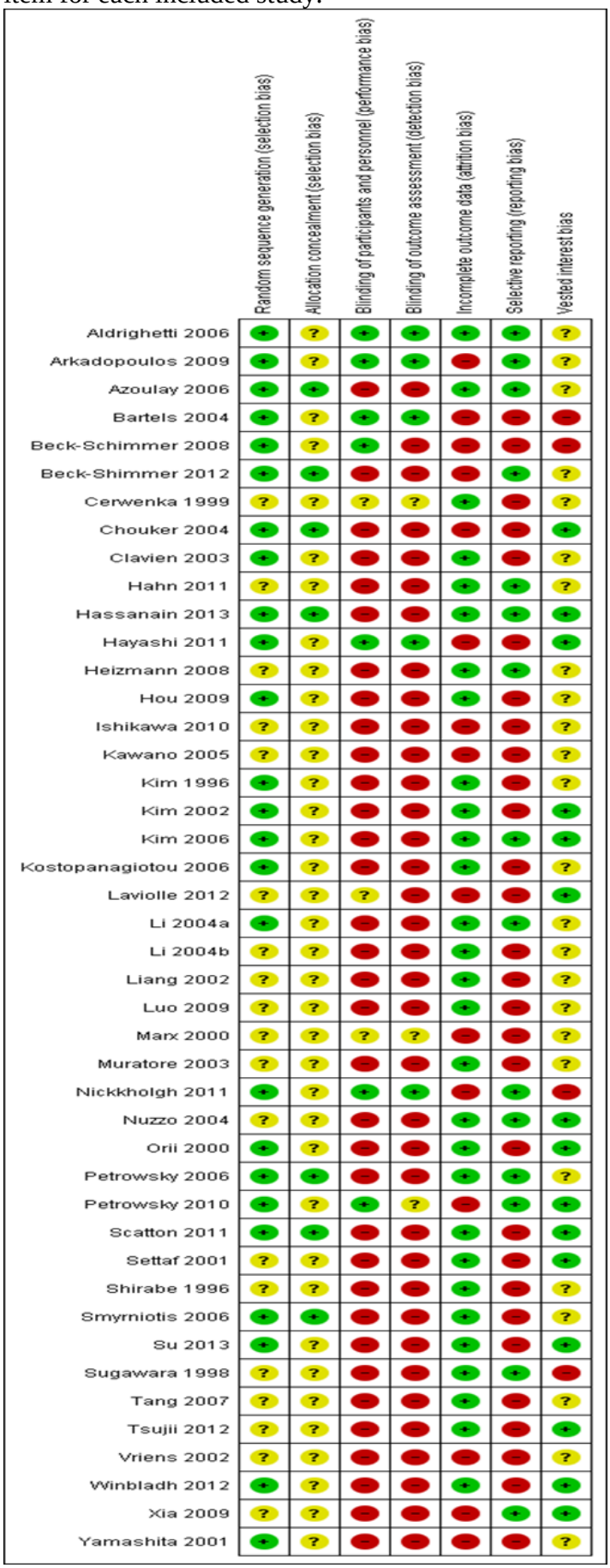
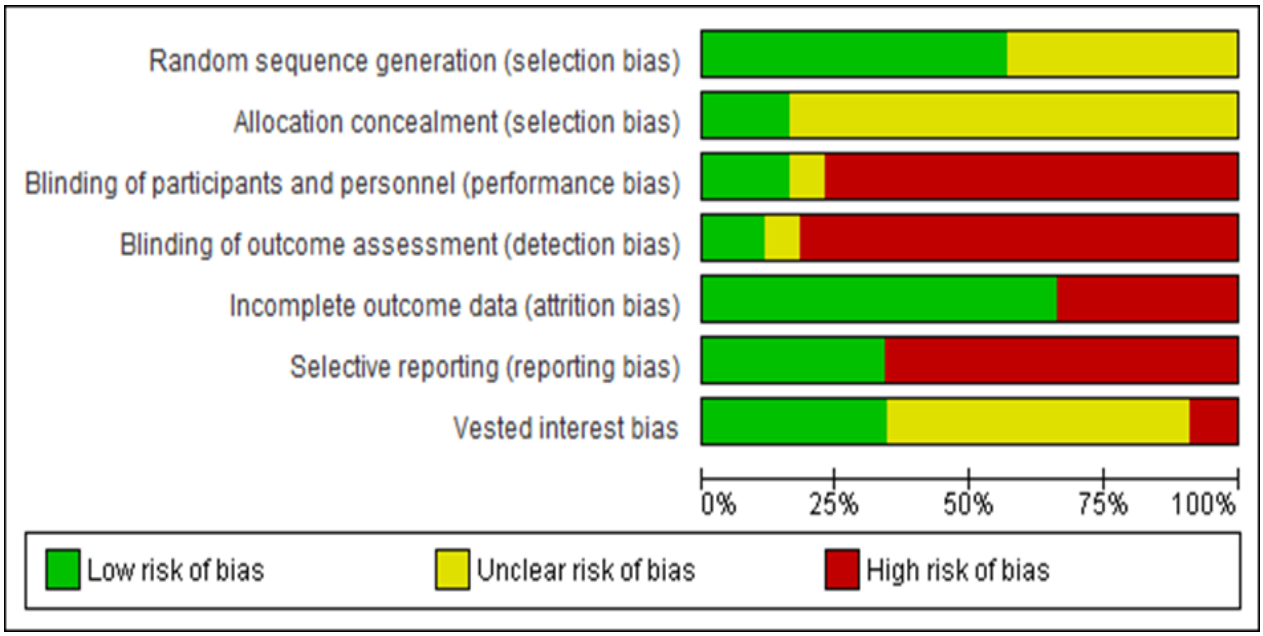


Figure A.3: Risk of bias graph - review authors' judgments about each risk of bias item presented as percentages across all included studies.



A.3.2. Overall network meta-analysis

A network meta-analysis was performed to compare the eight classes of active interventions aimed at decreasing IR injury along with the control group undergoing liver resection surgery alone. The classes of intervention were grouped based on their mechanism of action: hypothermia, ischaemic preconditioning, antioxidants, immunomodulators, cardiovascular modulators, steroids, treatments that increase hepatic glycogen, and miscellaneous therapies (Table A.3). None of the included trials compared ischaemic postconditioning to any other active or inactive intervention. Also, none of the included trials reported on quality of life, time needed to return to work, and the proportion of people who developed major blood loss.

Table A.3: Types of network meta-analyses performed. An overall network meta-analysis was performed to compare eight classes of active interventions aimed at decreasing IR injury along with a control group which was surgery alone. The classes of intervention were grouped based on their mechanism of action. The first sensitivity network meta-analysis was performed to compare all the individual interventions included in each class of intervention aimed at decreasing IR injury. The second sensitivity network meta-analysis was performed to compare the following 4 larger groups: surgery alone, hypothermia, ischaemic preconditioning, and all pharmacological interventions.

Overall network meta-analysis	First sensitivity network meta-analysis	Second sensitivity network meta-analysis
Surgery alone	Surgery alone	Surgery alone
Hypothermia	Hypothermia	Hypothermia
Ischaemic preconditioning	Ischaemic preconditioning	Ischaemic preconditioning
Antioxidants	Allopurinol	Pharmacological interventions
	Antioxidant multivitamin	
	Mannitol	
	Melatonin	
	Propofol	
	Vitamin E	
Cardiovascular modulators	Amrinone	
	Dopamine	
	Dopexamine	
	OKY 046	
	Trimetazidine	
	Verapamil	
Immunomodulators	Gabexate mesilate	
	Pentoxifylline	
	Prostaglandin E1	
	Sivelestat	
Increased hepatic glycogen	Insulin	
	Pre-storing hepatocellular glycogen	
Steroids	Steroids	
Miscellaneous	Branched chain amino acids	
	Desflurane	
	S-adenosyl-L-methionine	
	Sevoflurane	
	Ulinastatin	

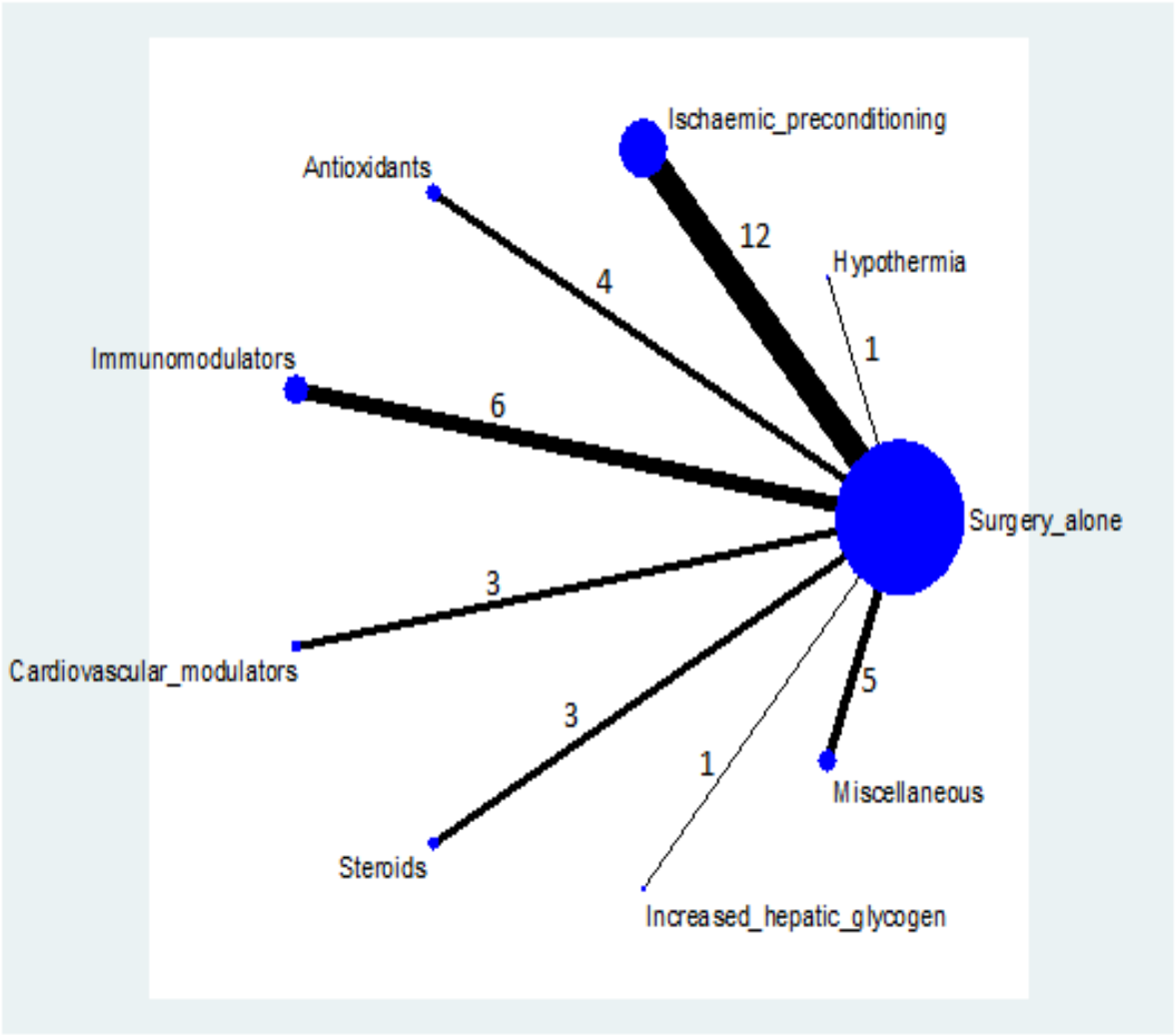
A.3.2.1. Mortality

Thirty five trials (2132 participants; 9 groups) provided data on mortality for the network meta-analysis.[68, 76, 78-80, 83-86, 91, 258, 317, 365, 366, 369-371, 373-385, 387-391] Nine trials, [67, 82, 87-90, 367, 372, 386] reporting on 325 patients, did not clearly report on mortality, and were excluded from the analysis of this outcome. In total, there were 28 deaths in the included trials giving an overall mortality of 1.3%. The fixed-effect model was preferred based on the DIC statistics, and there was no evidence of inconsistency in the networks. The pairwise odds ratios of the different treatment comparisons for mortality are shown in Table A.4. As shown in Table A.4, no significant difference was identified in mortality between the different groups. The network plot for mortality is shown in Figure A.4. Figures A.5 and A.6 show that none of the interventions was conclusively the best with more than 90% probability and there was a lot of uncertainty about the treatment with the lowest or highest mortality.

Table A.4: Pairwise odds ratios (OR) of the different treatment comparisons for the outcome mortality (95% confidence intervals). There was no statistically significant difference between the intervention groups for the outcome mortality.

Mortality Pairwise Odds Ratios								
	Hypothermia	**Ischaemic preconditioning**	**Antioxidants**	**Immuno-modulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	OR 1 (0-496.69)	OR 0.79 (0.35-1.74)	OR 0.57 (0.1-3.22)	OR 0.48 (0.13-1.81)	OR 0.94 (0.11-7.77)	OR 1.04 (0.07-15.27)	OR 0.92 (0-447.76)	OR 0.91 (0.15-5.55)
Hypothermia	-	OR 0.79 (0-413.14)	OR 0.57 (0-359.89)	OR 0.49 (0-278.45)	OR 0.94 (0-665.79)	OR 1.04 (0-905.42)	OR 0.93 (0-5933.5)	OR 0.91 (0-588.75)
Ischaemic preconditioning	-	-	OR 0.72 (0.11-4.88)	OR 0.62 (0.13-2.88)	OR 1.2 (0.12-11.44)	OR 1.32 (0.08-21.83)	OR 1.18 (0-600.13)	OR 1.16 (0.16-8.37)
Antioxidants	-	-	-	OR 0.85 (0.1-7.56)	OR 1.65 (0.11-25.48)	OR 1.83 (0.07-44.89)	OR 1.63 (0-1002.19)	OR 1.6 (0.13-19.67)
Immuno-modulators	-	-	-	-	OR 1.94 (0.16-23.38)	OR 2.14 (0.11-42.78)	OR 1.9 (0-1061.41)	OR 1.88 (0.2-17.61)
Cardiovascular modulators	-	-	-	-	-	OR 1.1 (0.04-33.77)	OR 0.98 (0-677.45)	OR 0.97 (0.06-15.64)
Steroids	-	-	-	-	-	-	OR 0.89 (0-755.15)	OR 0.88 (0.03-22.41)
Increased hepatic glycogen	-	-	-	-	-	-	-	OR 0.99 (0-618.89)

Figure A.4: Network plot of the interventions aiming to decrease hepatic IR injury for the outcome mortality.



Footnotes: circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison, also represented by the numbers in this figure.

Figure A.5: Probability of being best intervention for the outcome mortality. None of the interventions ranked best with more than 90% probability, and there is a lot of uncertainty about the intervention with the lowest mortality.

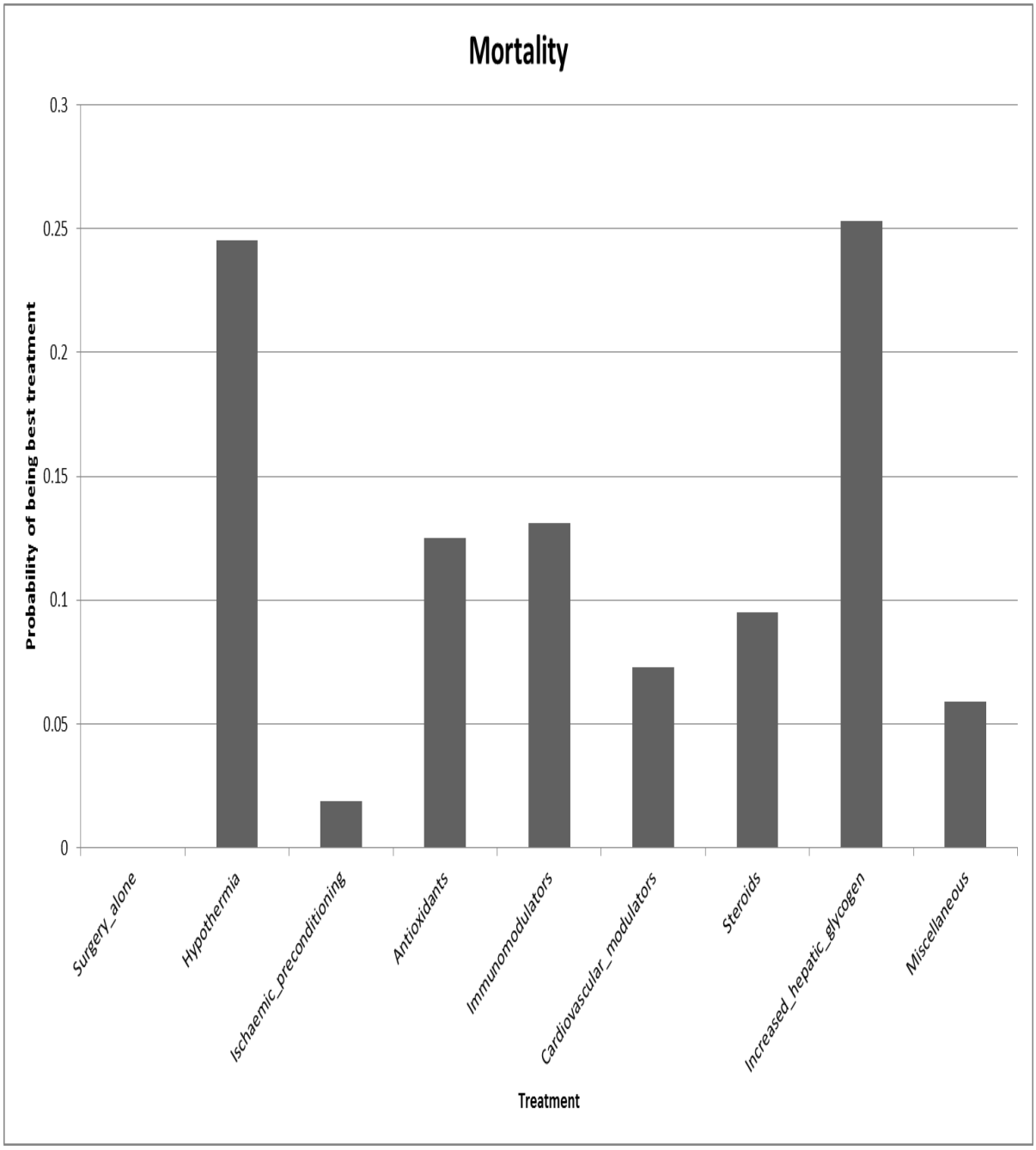
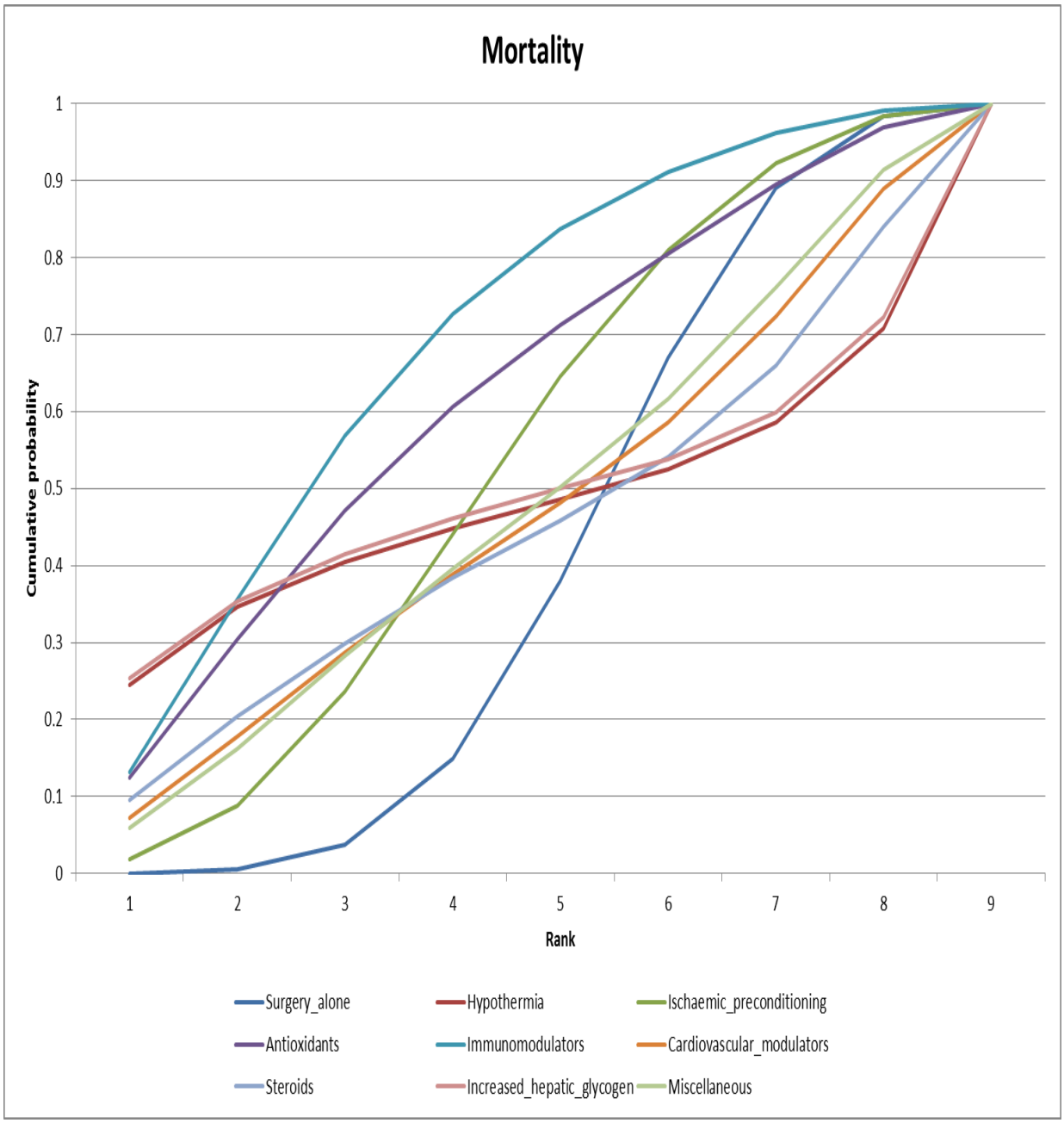


Figure A.6: Cumulative probability of ranks of different interventions aiming to decrease hepatic IR injury for the outcome mortality. There is substantial uncertainty about the intervention with the lowest or highest mortality.



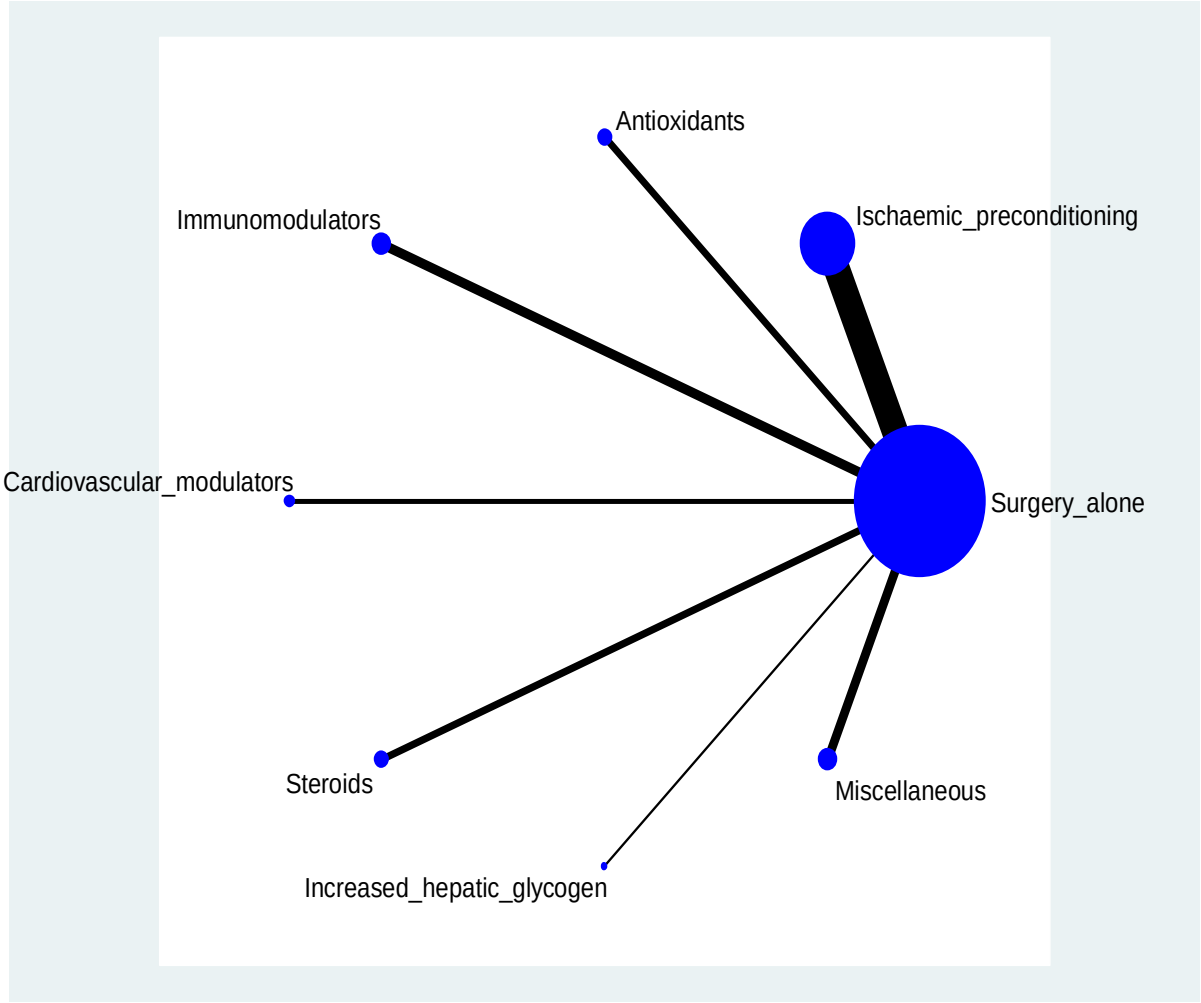
A.3.2.2. Serious adverse events

Twenty-eight trials (1887 participants; 8 groups) provided data on serious adverse events for the network meta-analysis. [68, 76, 79, 80, 82-84, 86, 91, 258, 317, 365-367, 369-373, 375, 376, 378, 379, 381, 382, 384, 385, 387] In total, there were 325 people with serious adverse events in the included trials (17.2%). Although some patients develop multiple serious adverse events postoperatively, most RCTs included in this review reported this outcome as number of patients rather than as number of events, therefore, this outcome was analysed as number of patients. The fixed-effect model was preferred based on the DIC statistics, and there was no evidence of inconsistency. The pairwise odds ratios of the different treatment comparisons for serious adverse events are shown in Table A.5. Significantly fewer serious adverse events were found in the ischaemic preconditioning group compared to the surgery alone group. Also, there were significantly fewer serious adverse events in the cardiovascular modulators group compared to surgery alone. Furthermore, significantly fewer serious adverse events were found in the miscellaneous group compared to surgery alone, ischaemic preconditioning, immunomodulators, and steroids. There was no significant difference in the other comparisons. The network plot for serious adverse events is shown in Figure A.7. Figures A.8 and A.9 show that although the miscellaneous group had a high probability (74.2%) of being the best treatment for this outcome, none of the treatment groups ranked best with more than 90% probability and there was a lot of uncertainty about the treatment group with the fewest or with the most serious adverse events.

Table A.5: Pairwise odds ratios (OR) of the different treatment comparisons for the outcome serious adverse events (95% confidence intervals). Statistically significant results are in bold. Significantly fewer serious adverse events were found in the ischaemic preconditioning group compared to the surgery alone group. Also, there were significantly fewer serious adverse events in the cardiovascular modulators group compared to surgery alone. Furthermore, significantly fewer serious adverse events were found in the miscellaneous group compared to surgery alone, ischaemic preconditioning, immunomodulators, and steroids. There was no significant difference in the other comparisons.

	Ischaemic preconditioning	**Antioxidants**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	**OR 0.66 (0.44- 0.98)**	OR 0.54 (0.19-1.47)	OR 0.67 (0.34-1.34)	**OR 0.39 (0.18-0.87)**	OR 0.66 (0.32-1.35)	OR 0.69 (0.15-3.08)	**OR 0.21 (0.08-0.51)**
Ischaemic preconditioning	-	OR 0.82 (0.27-2.43)	OR 1.03 (0.46-2.28)	OR 0.6 (0.24-1.47)	OR 1 (0.44-2.28)	OR 1.05 (0.22-4.96)	**OR 0.31 (0.12-0.85)**
Antioxidants	-	-	OR 1.26 (0.37-4.28)	OR 0.73 (0.2-2.67)	OR 1.23 (0.36-4.25)	OR 1.28 (0.21-7.85)	OR 0.38 (0.1-1.5)
Immunomodulators	-	-	-	OR 0.58 (0.2-1.68)	OR 0.98 (0.36-2.65)	OR 1.02 (0.2-5.34)	**OR 0.31 (0.1-0.96)**
Cardiovascular modulators	-	-	-	-	OR 1.68 (0.57-4.92)	OR 1.75 (0.32-9.62)	OR 0.53 (0.16-1.76)
Steroids	-	-	-	-	-	OR 1.04 (0.2-5.51)	**OR 0.31 (0.1-0.99)**
Increased hepatic glycogen	-	-	-	-	-	-	OR 0.3 (0.05-1.74)

Figure A.7: Network plot of the interventions aiming to decrease hepatic IR injury for the outcome serious adverse events.



Footnotes: circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison.

Figure A.8: Probability of being best intervention for the outcome serious adverse events. Although the miscellaneous group had a high probability (74.2%) of being the best intervention for this outcome, none of the interventions ranked best with more than 90% probability.

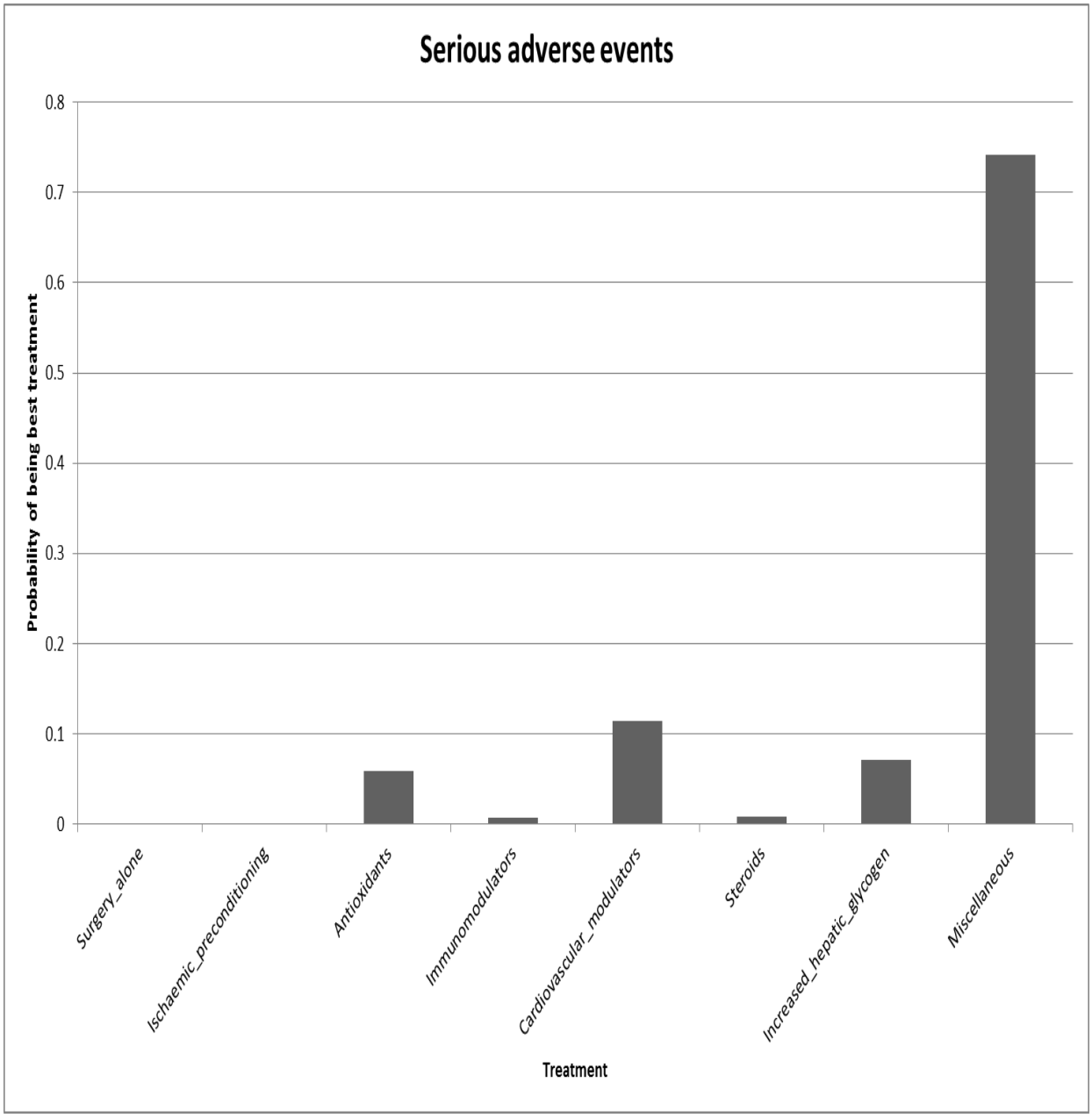
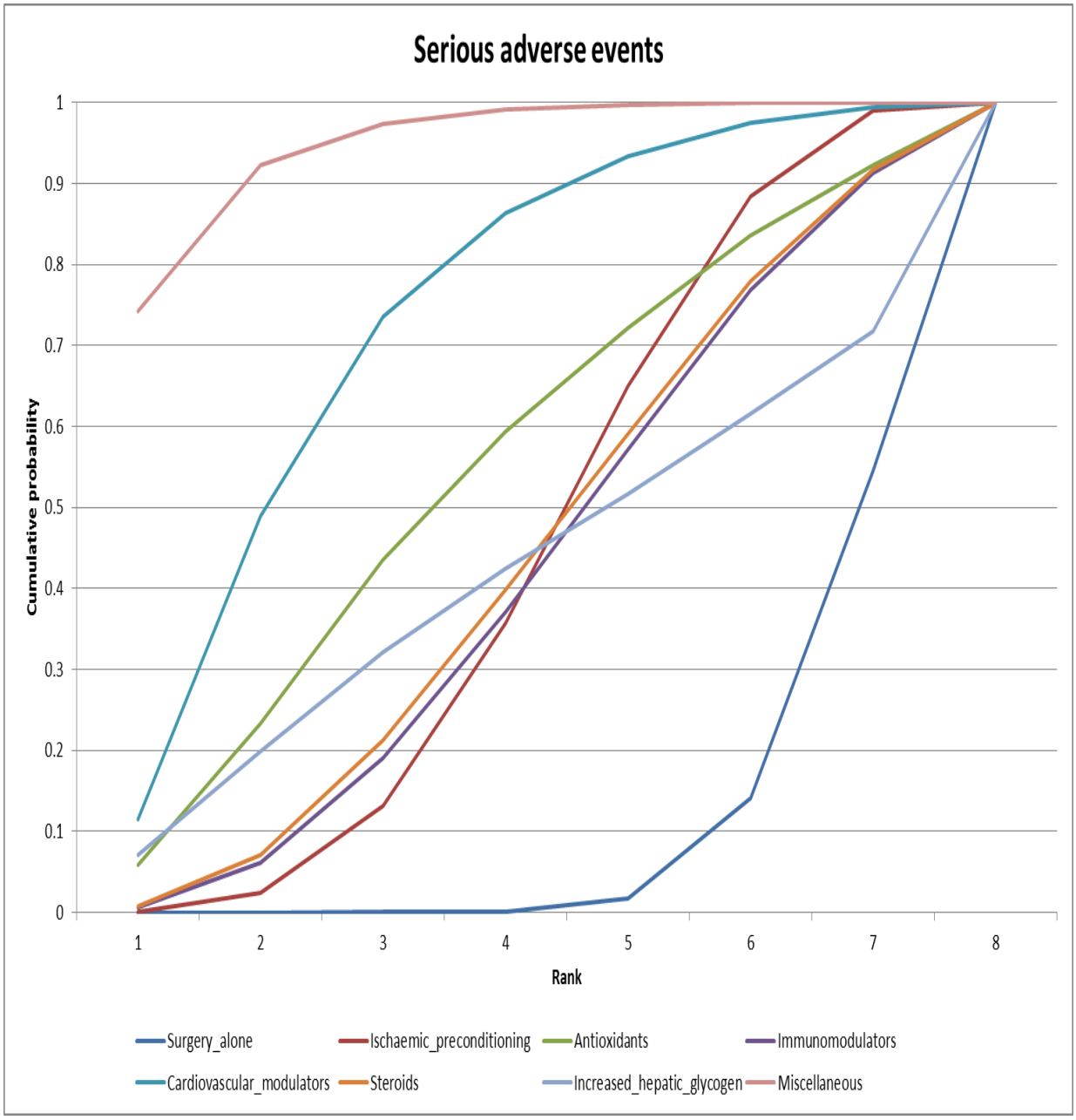


Figure A.9: Cumulative probability of ranks of different interventions aiming to decrease hepatic IR injury for the outcome serious adverse events. There was a lot of uncertainty about the intervention group with the fewest or with the most serious adverse events.



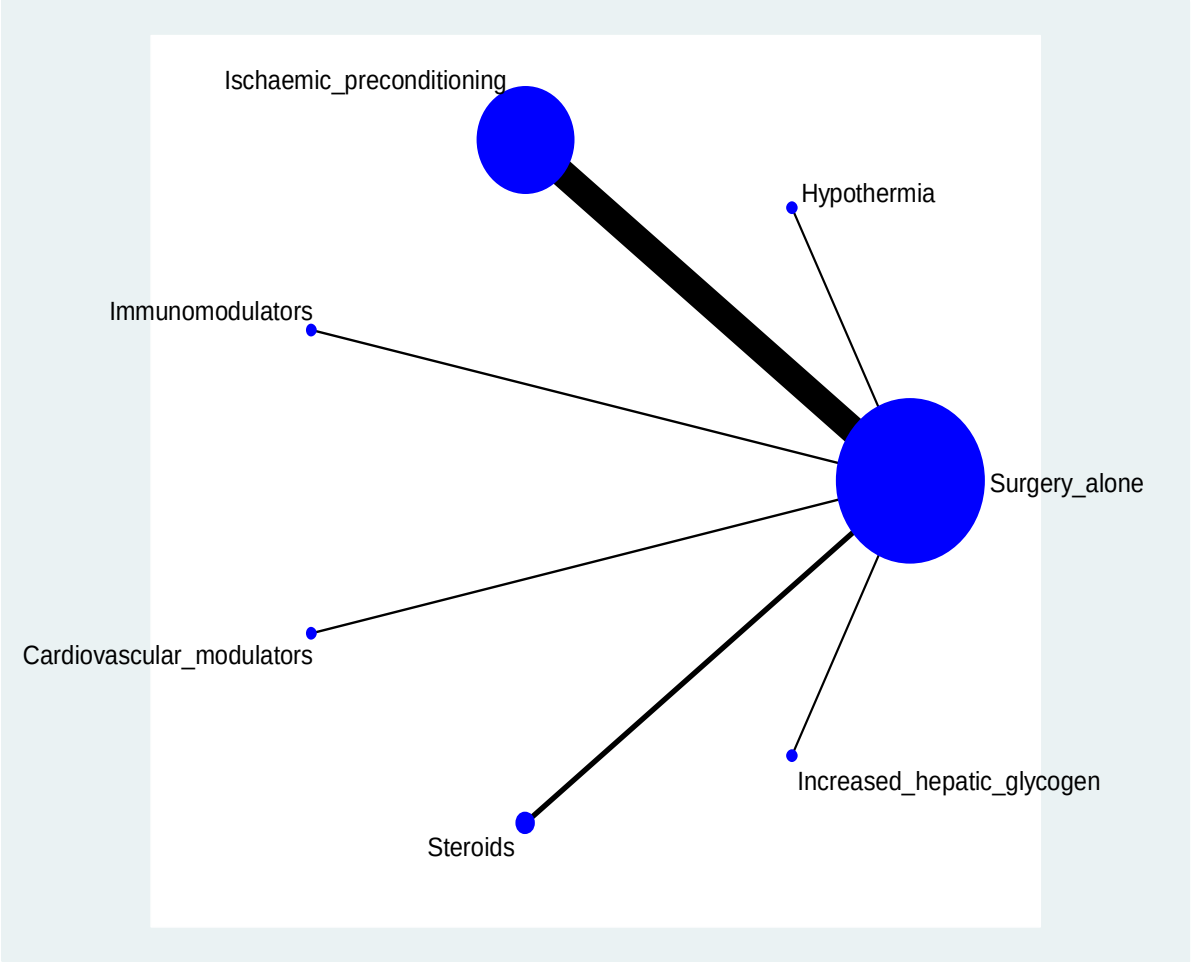
A.3.2.3. Proportion of patients transfused perioperatively

Seventeen trials provided data on the proportion of patients transfused for the network meta-analysis.[67, 68, 76, 78-80, 85, 87, 91, 258, 317, 365, 366, 371, 372, 382, 384] One trial[87] was excluded because it was not connected to the network plot with the other studies for this outcome. Thus leaving 16 trials [67, 68, 76, 78-80, 85, 91, 258, 317, 365, 366, 371, 372, 382, 384] for analysis on 1261 participants divided in 7 groups. In total, 294 people had blood transfusion in the included trials (23.3%). The fixed-effect model was preferred and there was no evidence of inconsistency in the network. The results of the pairwise comparisons for the proportion of patients transfused are provided in Table A.6. Pairwise comparison of the interventions showed that significantly fewer people were transfused with ischaemic preconditioning compared to steroids. There was no significant difference in the other comparisons. The network plot for the proportion of patients transfused is shown in Figure A.10. Figures A.11 and A.12 show that none of the treatment groups ranked best with more than 90% probability and there was a lot of uncertainty about the treatment group with the lowest and with the highest proportion of patients transfused.

Table A.6: Pairwise odds ratios (OR) of the different treatment comparisons for the outcome proportion of patients transfused (95% confidence intervals). Statistically significant results are in bold. Pairwise comparison of the interventions showed that significantly fewer people were transfused with ischaemic preconditioning compared to steroids. There was no significant difference in the other comparisons.

	Hypothermia	**Ischaemic preconditioning**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**
Surgery alone	OR 3.16 (0.35-28.39)	OR 0.71 (0.5-1)	OR 0.65 (0.18-2.29)	OR 0.84 (0.35-2.01)	OR 1.63 (0.79-3.38)	OR 1.02 (0.35-3.03)
Hypothermia	-	OR 0.22 (0.02-2.07)	OR 0.21 (0.02-2.59)	OR 0.27 (0.02-2.83)	OR 0.52 (0.05-5.23)	OR 0.32 (0.03-3.76)
Ischaemic preconditioning	-	-	OR 0.92 (0.25-3.41)	OR 1.19 (0.46-3.05)	**OR 2.31 (1.03-5.18)**	OR 1.45 (0.46-4.54)
Immunomodulators	-	-	-	OR 1.29 (0.28-6.02)	OR 2.51 (0.58-10.81)	OR 1.58 (0.3-8.36)
Cardiovascular modulators	-	-	-	-	OR 1.94 (0.62-6.08)	OR 1.22 (0.3-4.93)
Steroids	-	-	-	-	-	OR 0.63 (0.17-2.32)

Figure A.10: Network plot of the interventions aiming to decrease hepatic IR injury for the outcome proportion of patients transfused.



Footnotes: circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison.

Figure A.11: Probability of being best intervention for the outcome proportion of patients transfused. None of the interventions ranked best with more than 90% probability.

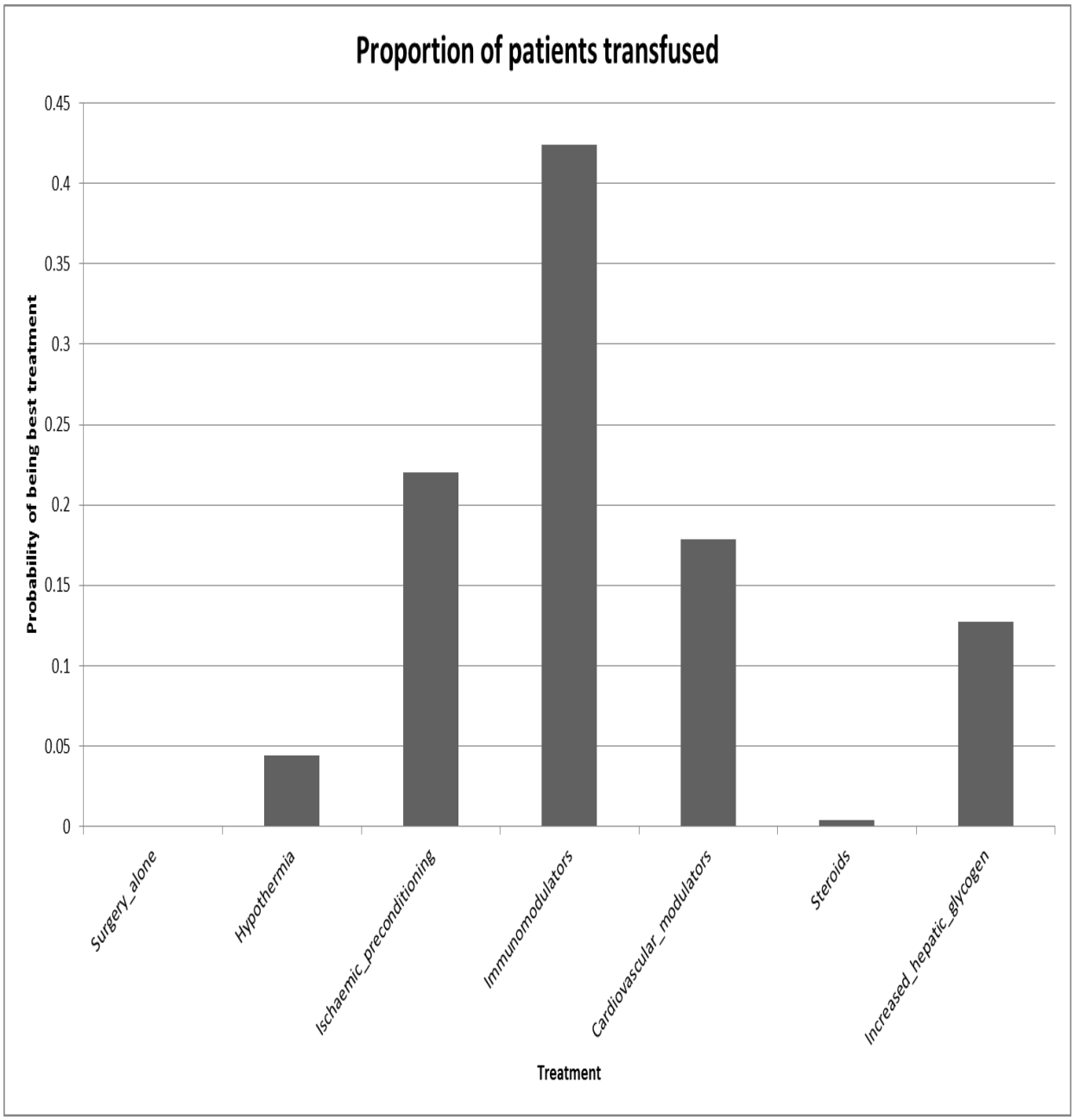
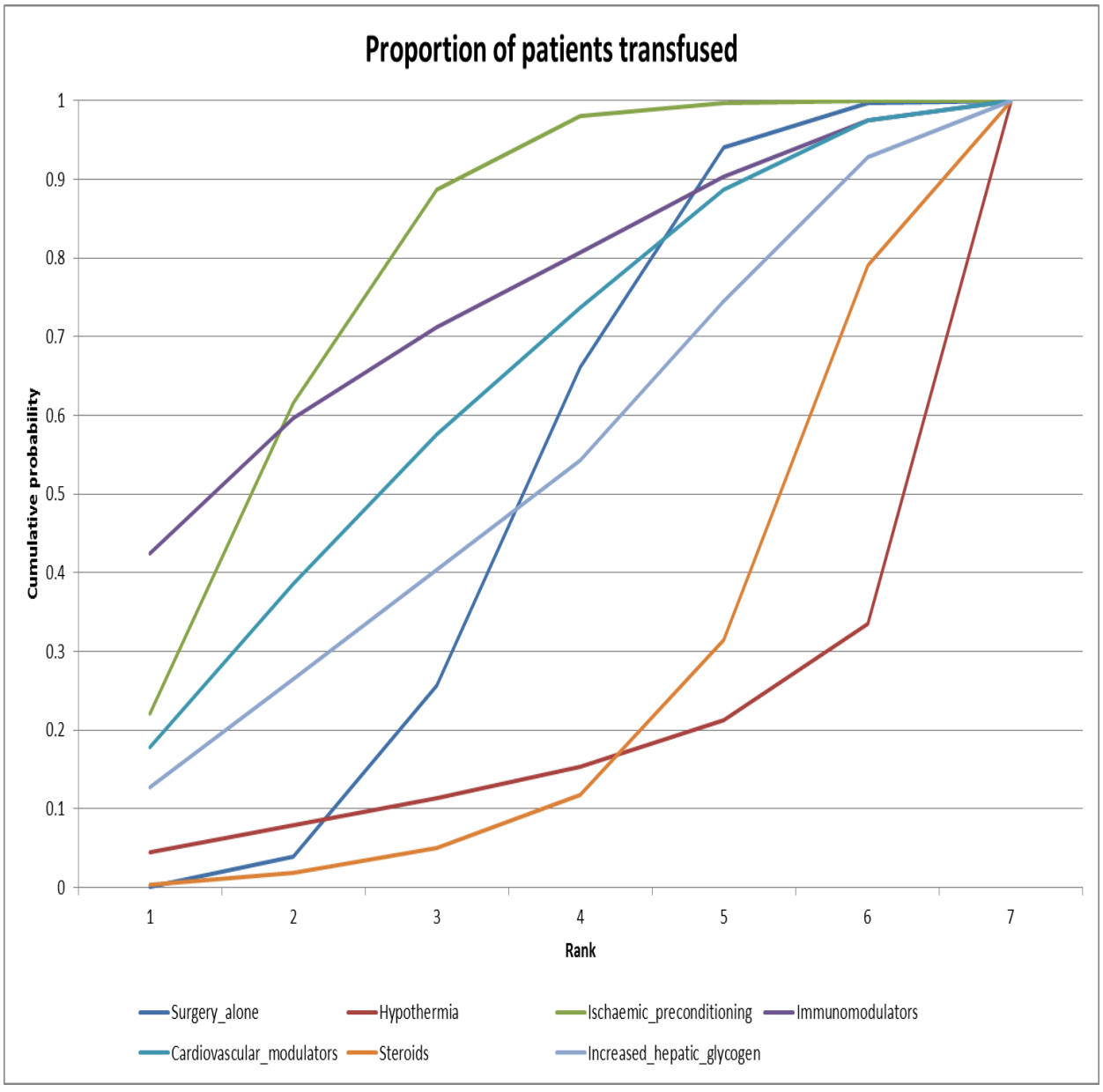


Figure A.12: Cumulative probability of ranks of different interventions aiming to decrease hepatic IR injury for the outcome proportion of patients transfused. There was a lot of uncertainty about the intervention group with the lowest and with the highest proportion of patients transfused.



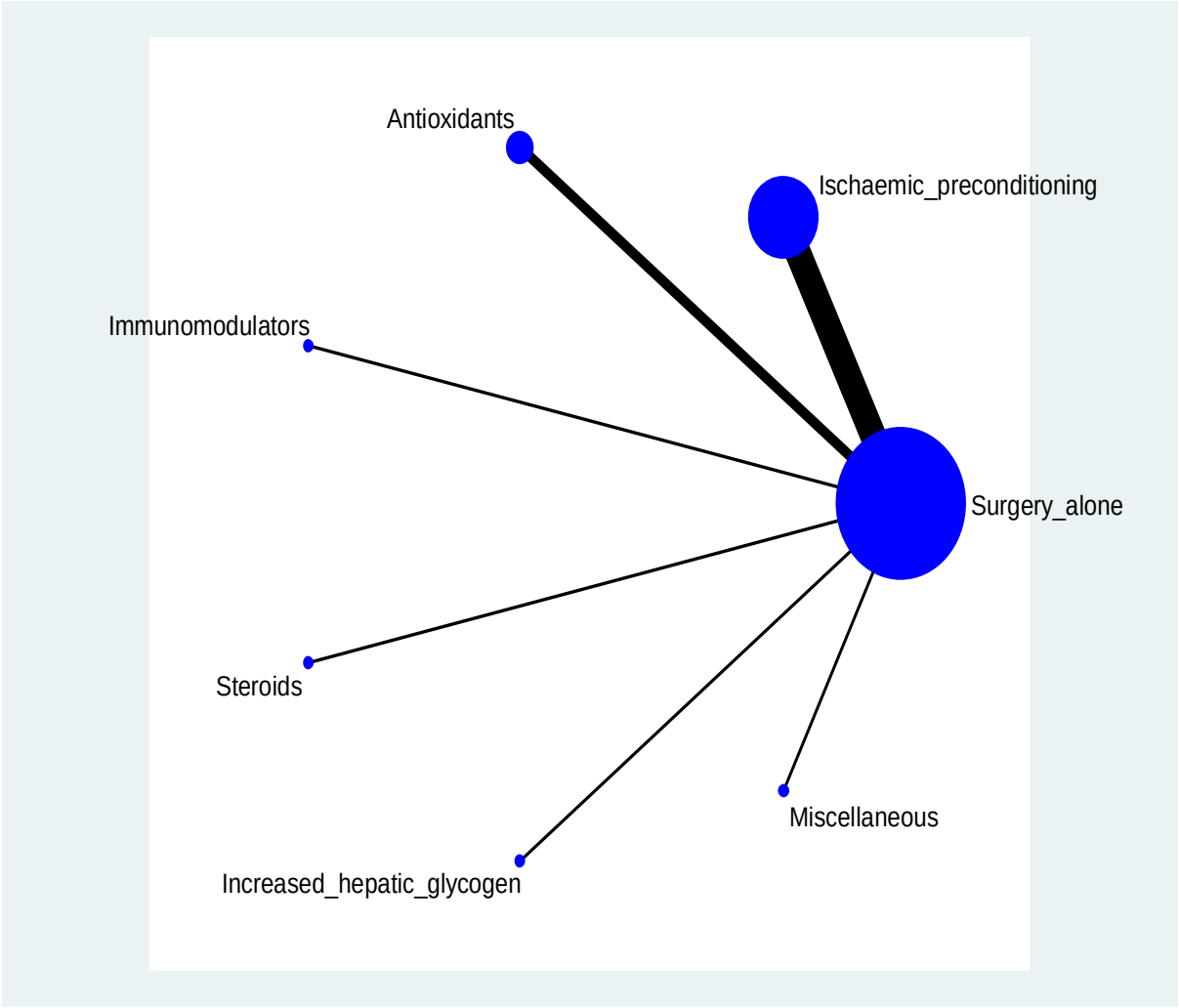
A.3.2.4. Perioperative quantity of blood transfusion per patient

Fourteen trials[76, 79, 80, 86, 258, 260, 365, 369, 371, 375, 377, 381, 382, 387] (901 participants; 7 groups) were included in the analysis. On average, 1.4 units of blood were transfused per patient. The random-effects model was preferred based on the DIC statistics, and there was no evidence of inconsistency in the networks. The results of the pairwise comparisons for the quantity of blood transfusion per patient are provided in Table A.7. No evidence of any significant difference in quantity of blood transfusion per patient between the different interventions was found with pairwise comparison. The network plot for quantity of blood transfusion per patient is shown in Figure A.13. Figures A.14 and A.15 show that none of the treatment groups ranked best with more than 90% probability and there was a lot of uncertainty about the treatment group with the lowest and with the highest quantity of blood transfusion per patient.

Table A.7: Pairwise mean differences (MD) of the different treatment comparisons for the outcome quantity of blood transfusion per patient (95% confidence intervals). There was no statistically significant difference between the intervention groups for this outcome.

	Ischaemic preconditioning	**Antioxidants**	**Immunomodulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	MD -0.1 (-1.28 to 1.08)	MD -0.54 (-2.45 to 1.37)	MD -0.31 (-3.57 to 2.96)	MD -0.79 (-3.96 to 2.38)	MD -0.01 (-3.15 to 3.14)	MD 0.01 (-3.13 to 3.16)
Ischaemic preconditioning	-	MD -0.44 (-2.69 to 1.81)	MD -0.21 (-3.68 to 3.27)	MD -0.69 (-4.07 to 2.7)	MD 0.09 (-3.26 to 3.45)	MD 0.11 (-3.25 to 3.47)
Antioxidants	-	-	MD 0.23 (-3.55 to 4.02)	MD -0.25 (-3.95 to 3.45)	MD 0.53 (-3.15 to 4.21)	MD 0.55 (-3.13 to 4.23)
Immunomodulators	-	-	-	MD -0.48 (-5.04 to 4.07)	MD 0.3 (-4.24 to 4.83)	MD 0.32 (-4.22 to 4.85)
Steroids	**-**	**-**	**-**	**-**	MD 0.78 (-3.68 to 5.24)	MD 0.8 (-3.67 to 5.27)
Increased hepatic glycogen	**-**	**-**	**-**	**-**	-	MD 0.02 (-4.43 to 4.46)

Figure A.13: Network plot of the interventions aiming to decrease hepatic IR injury for the outcome quantity of blood transfusion per patient.



Footnotes: circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison.

Figure A.14: Probability of being best intervention for the outcome quantity of blood transfusion per patient. None of the intervention groups ranked best with more than 90% probability.

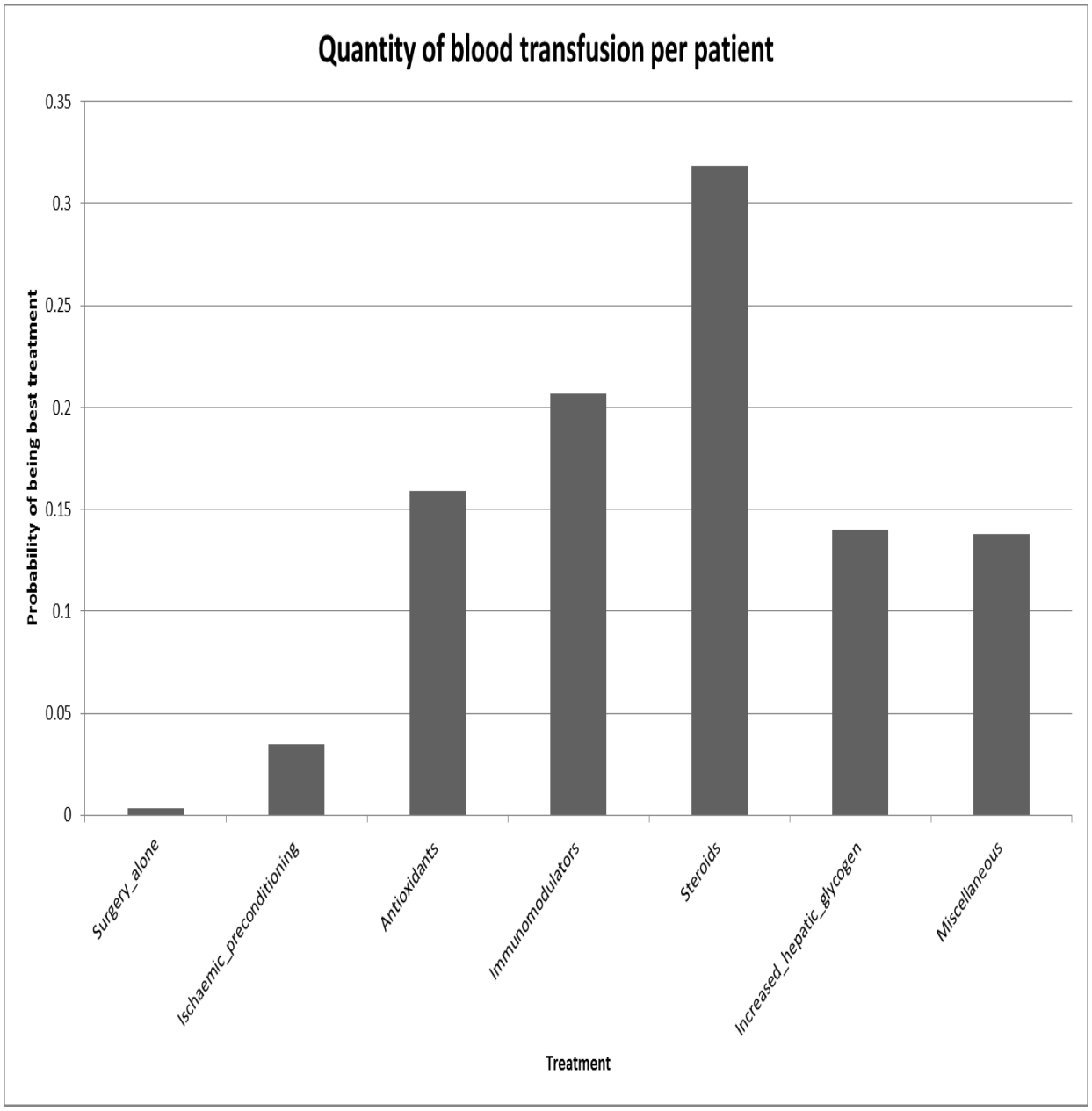
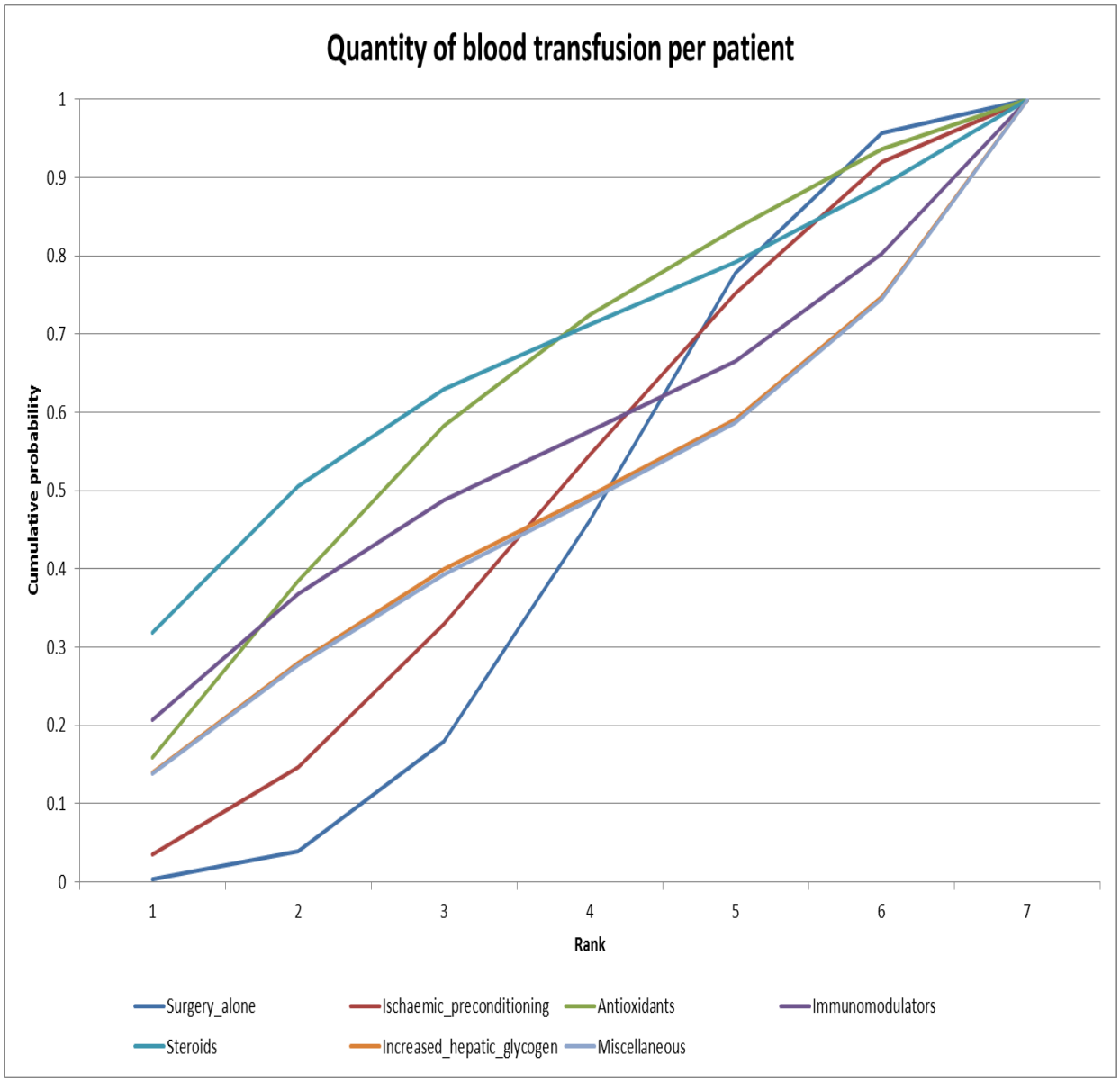


Figure A.15: Cumulative probability of ranks of different interventions aiming to decrease hepatic IR injury for the outcome quantity of blood transfusion per patient. There was a lot of uncertainty about the intervention group with the lowest and with the highest quantity of blood transfusion per patient.



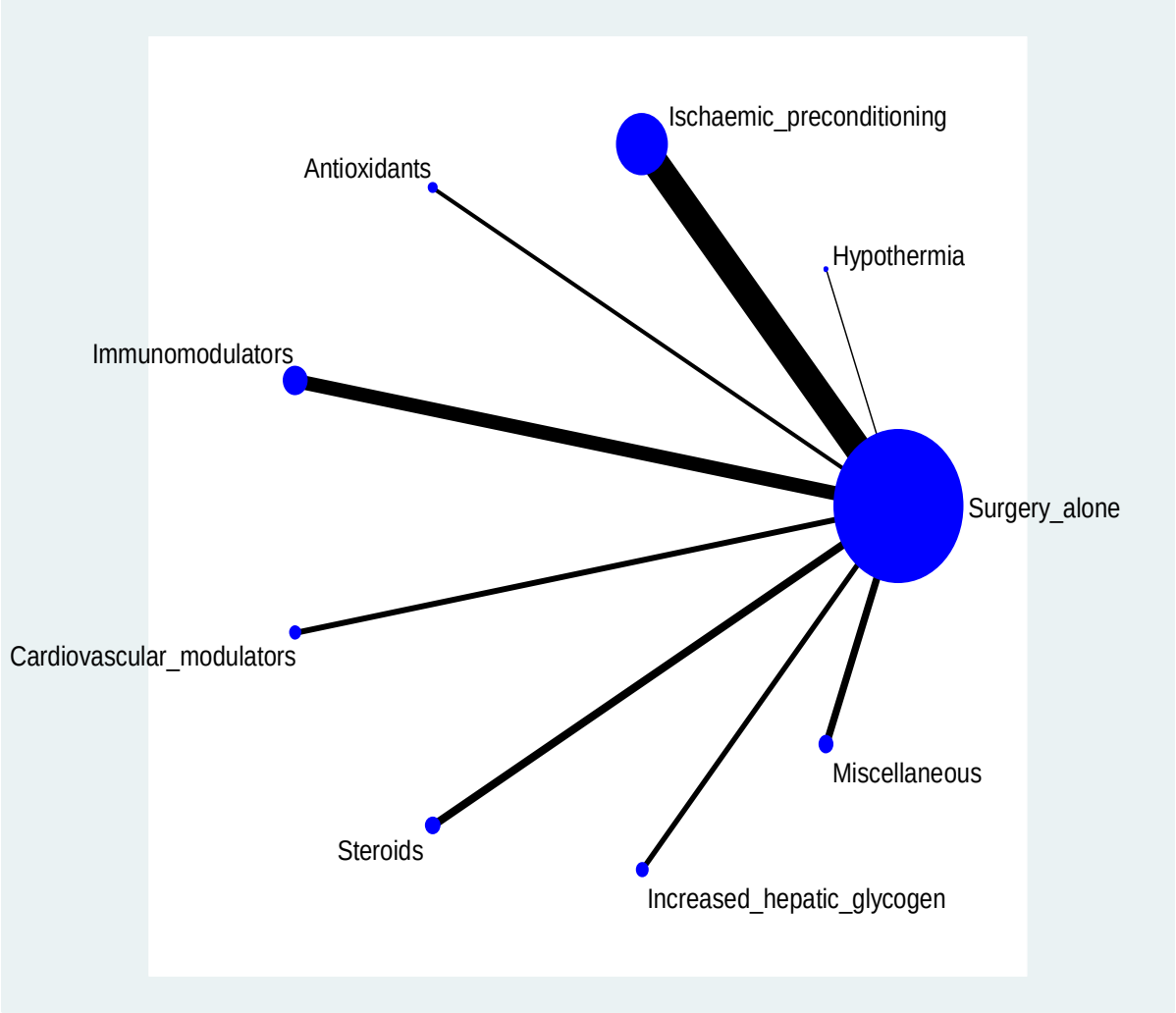
A.3.2.5. Operative blood loss during hepatectomy

Thirty six trials[67, 68, 76, 78-80, 83-86, 88, 89, 91, 258, 317, 365-367, 371-376, 378-381, 383, 384, 386-391] (2114 participants; 9 groups) were included in the analysis of this outcome. The fixed-effect model was preferred based on the DIC statistics, and there was no evidence of inconsistency in the networks. The results of the pairwise comparisons for operative blood loss are provided in Table A.8. The pairwise mean differences of the different group comparisons showed that ischaemic preconditioning had significantly lower operative blood loss compared to all other groups and ranked best treatment with 99.7% probability. Also, the surgery alone group had significantly lower operative blood loss compared to all other groups except ischaemic preconditioning, and ranked second best treatment with 98.5% probability. In addition, the steroids and increased hepatic glycogen groups were found to have significantly lower operative blood loss compared to the hypothermia, immunomodulators, and miscellaneous groups. The network plot for operative blood loss is shown in Figure A.16. Figures A.17 and A.18 show that ischaemic preconditioning ranked best, and surgery alone ranked second best, with more than 90% probability for operative blood loss. There was substantial uncertainty about the intervention ranking worst for operative blood loss.

Table A.8: Pairwise mean differences (MD) of the different treatment comparisons for the outcome operative blood loss (95% confidence intervals). Statistically significant results are in bold. The pairwise mean differences of the different group comparisons showed that ischaemic preconditioning had significantly lower operative blood loss compared to all other groups. Also, the surgery alone group had significantly lower operative blood loss compared to all other groups except ischaemic preconditioning. In addition, the steroids and increased hepatic glycogen groups were found to have significantly lower operative blood loss compared to the hypothermia, immunomodulators, and miscellaneous groups.

	Hypothermia	**Ischaemic preconditioning**	**Antioxidants**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	**MD 247.1 (143.59 to 350.61)**	**MD -35.97 (-53.76 to -18.18)**	**MD 207 (34.13 to 379.87)**	**MD 231.2 (145.82 to 316.58)**	**MD 142.2 (61.59 to 222.81)**	**MD 69.32 (21.46 to 117.18)**	**MD 92.04 (25.2 to 158.88)**	**MD 209.7 (118.32 to 301.08)**
Hypothermia	-	**MD -283.07 (-388.09 to -178.05)**	MD -40.1 (-241.59 to 161.39)	MD -15.9 (-150.08 to 118.28)	MD -104.9 (-236.1 to 26.3)	**MD -177.78 (-291.82 to -63.74)**	**MD -155.06 (-278.27 to -31.85)**	MD -37.4 (-175.47 to 100.67)
Ischaemic preconditioning	-	-	**MD 242.97 (69.19 to 416.75)**	**MD 267.17 (179.96 to 354.38)**	**MD 178.17 (95.62 to 260.72)**	**MD 105.29 (54.23 to 156.35)**	**MD 128.01 (58.85 to 197.17)**	**MD 245.67 (152.58 to 338.76)**
Antioxidants	-	-	-	MD 24.2 (-168.61 to 217.01)	MD -64.8 (-255.54 to 125.94)	MD -137.68 (-317.06 to 41.7)	MD -114.96 (-300.3 to 70.38)	MD 2.7 (-192.84 to 198.24)
Immunomodulators	-	-	-	-	MD -89 (-206.42 to 28.42)	**MD -161.88 (-259.76 to -64)**	**MD -139.16 (-247.59 to -30.73)**	MD -21.5 (-146.56 to 103.56)
Cardiovascular modulators	-	-	-	-	-	MD -72.88 (-166.63 to 20.87)	MD -50.16 (-154.88 to 54.56)	MD 67.5 (-54.35 to 189.35)
Steroids	-	-	-	-	-	-	MD 22.72 (-59.49 to 104.93)	**MD 140.38 (37.23 to 243.53)**
Increased hepatic glycogen	-	-	-	-	-	-	-	**MD 117.66 (4.45 to 230.87)**

Figure A.16: Network plot of the interventions aiming to decrease hepatic IR injury for the outcome operative blood loss.



Footnotes: circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison.

Figure A.17: Probability of being best intervention for the outcome operative blood loss. Ischaemic preconditioning ranked best intervention for this outcome with 99.7% probability.

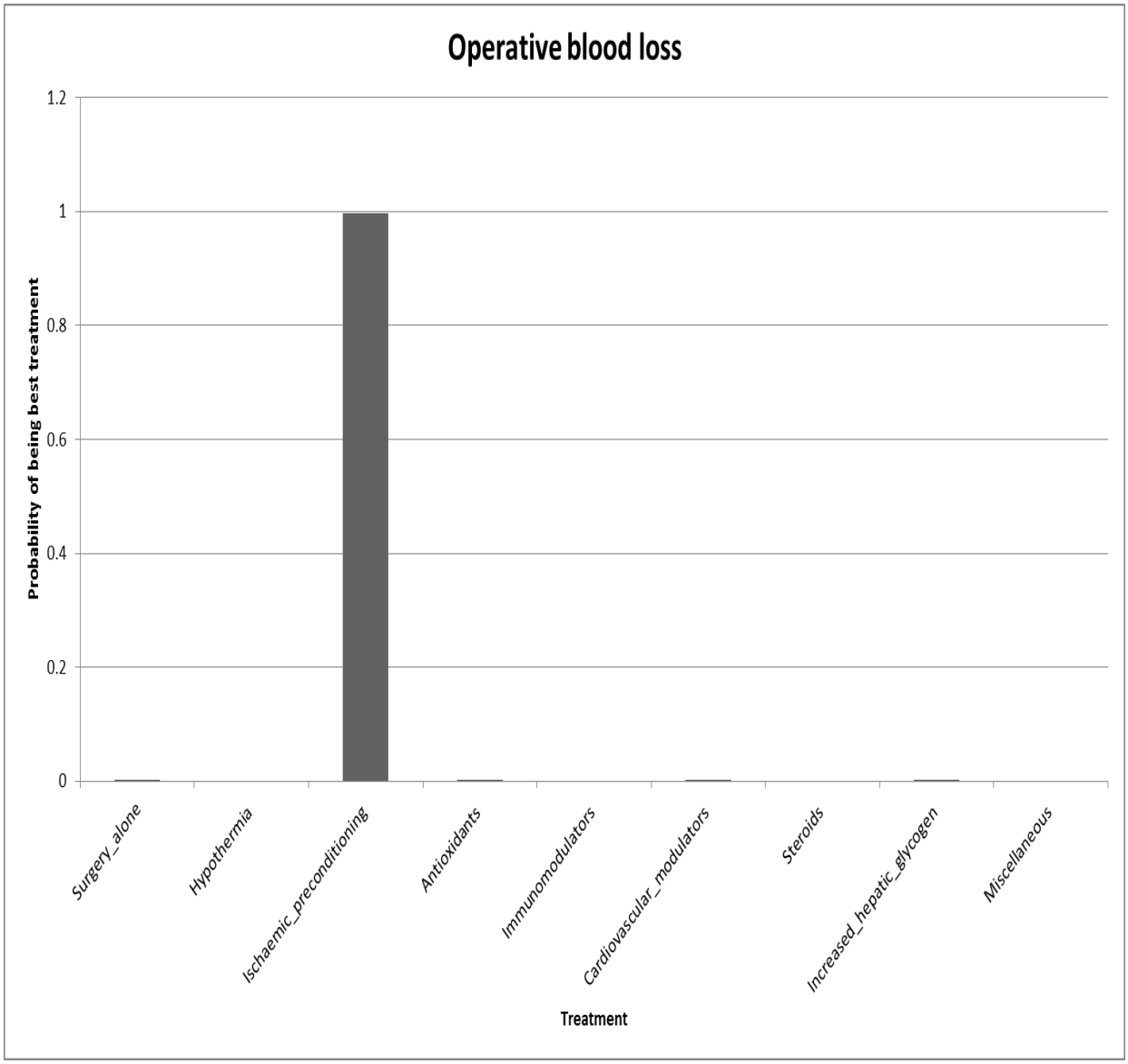
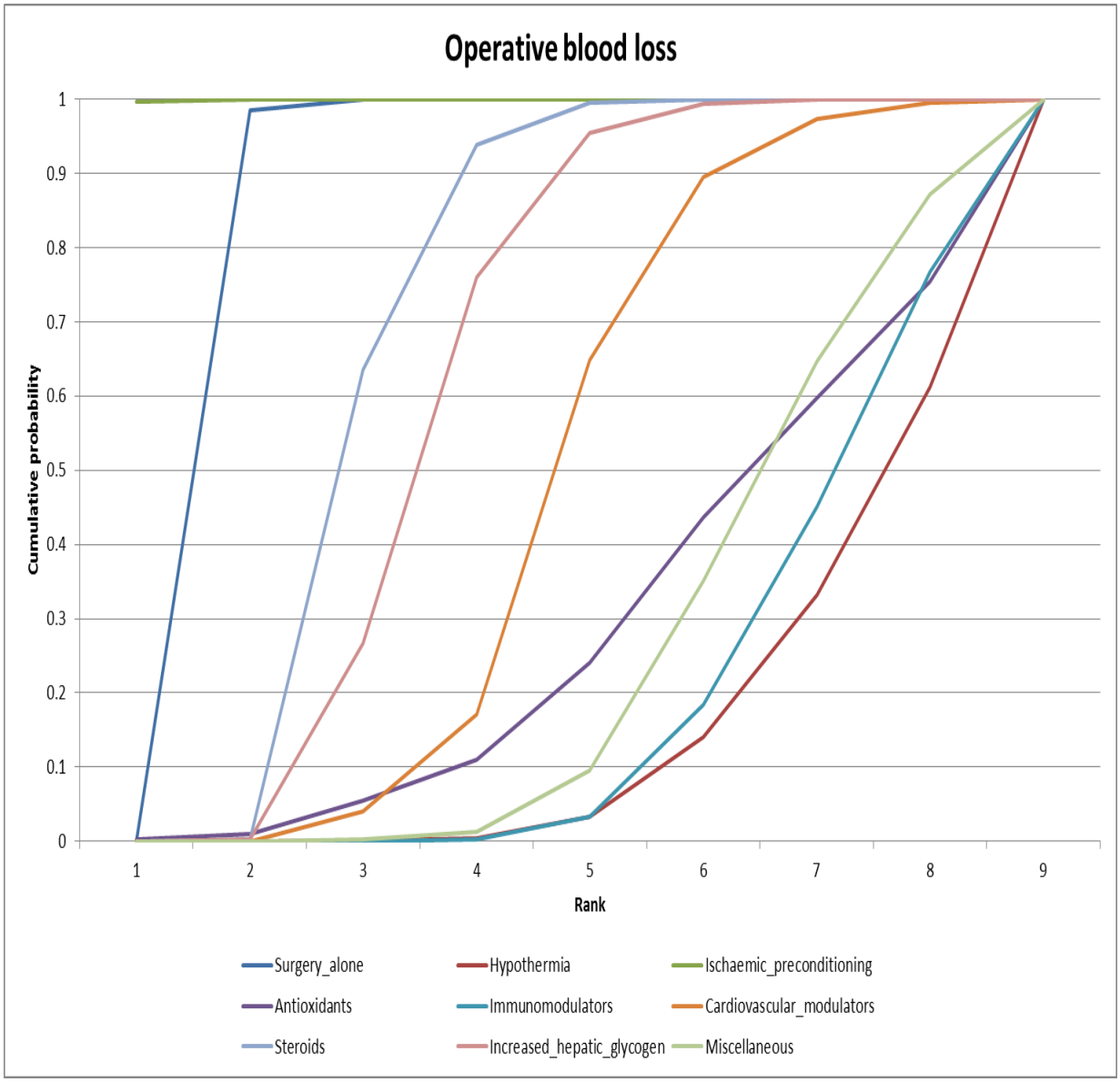


Figure A.18: Cumulative probability of ranks of different interventions aiming to decrease hepatic IR injury for the outcome operative blood loss. Ischaemic preconditioning ranked best intervention with more than 90% probability, and surgery alone ranked second best with more than 90% probability for operative blood loss. There was substantial uncertainty about the intervention ranking worst for operative blood loss.



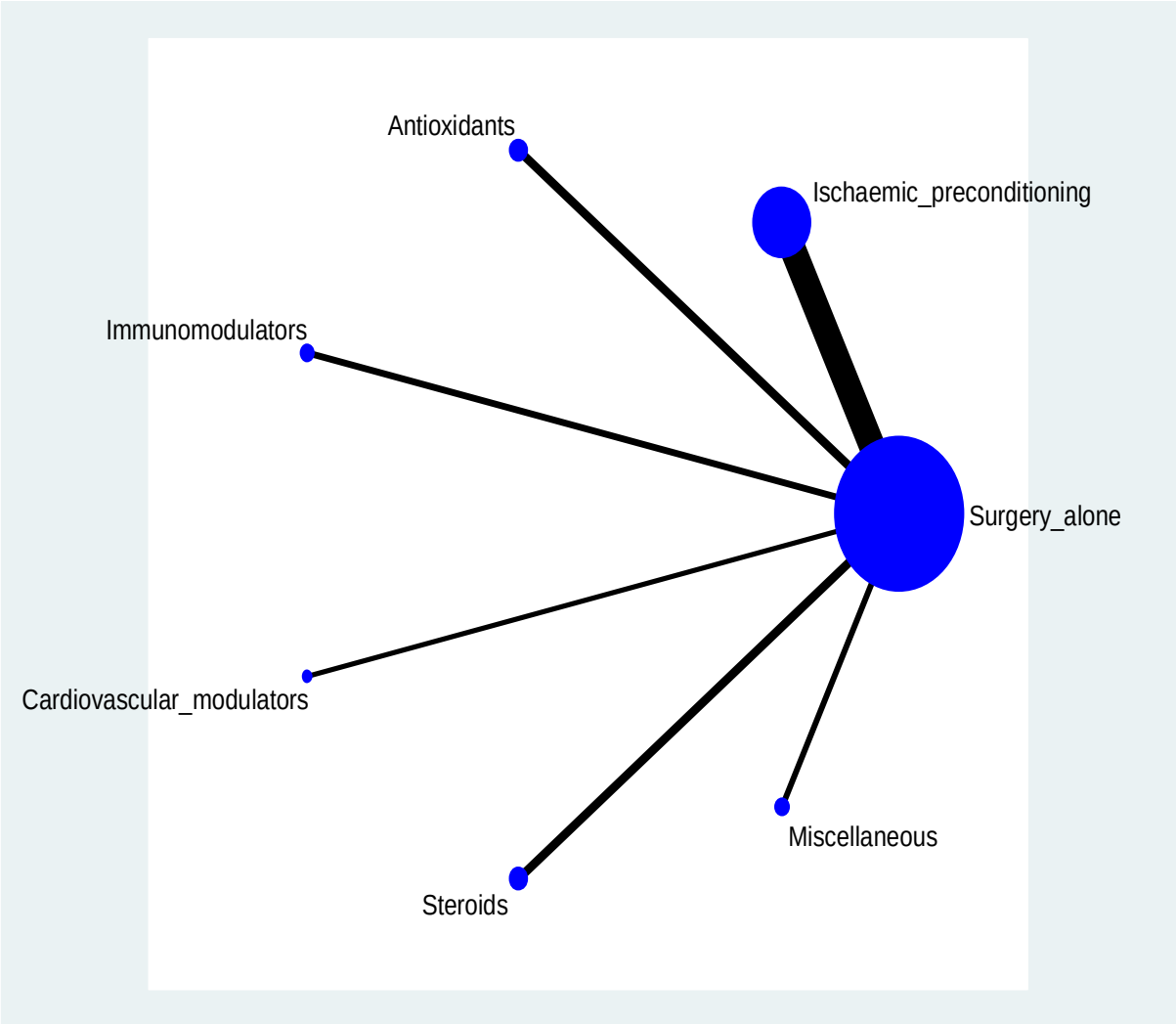
A.3.2.6. Postoperative length of hospital stay

Twenty seven trials (1610 participants; 7 groups) provided data for the network meta-analysis on IR therapy during hepatectomy and the length of hospital stay.[68, 76, 79, 80, 83-86, 91, 258, 317, 366, 367, 369, 370, 372, 374, 377-381, 384, 385, 387, 390, 391] The average length of hospital stay was 13.7 days. The random-effects model was preferred based on the DIC statistics and there was no evidence of inconsistency in the networks. The results of the pairwise comparisons for length of hospital stay are provided in Table A.9. The pairwise comparison of the interventions showed ischaemic preconditioning to have significantly shorter length of hospital stay compared to surgery alone by 2.3 days (MD -2.34, 95% CrI -4.06 to -0.62). There was no significant difference in the other comparisons. The network plot for length of hospital stay is shown in Figure A.19. Figures A.20 and A.21 show that no class of interventions ranked best with more than 90% probability, and there was substantial uncertainty regarding the best or worst group of interventions for this outcome.

Table A.9: Pairwise mean differences (MD) of the different treatment comparisons for the outcome length of hospital stay (95% confidence intervals). Statistically significant results are in bold. The pairwise comparison of the interventions showed ischaemic preconditioning to have significantly shorter length of hospital stay compared to surgery alone. There was no significant difference in the other comparisons.

	Ischaemic preconditioning	**Antioxidants**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Miscellaneous**
Surgery alone	**MD -2.34 (-4.06 to -0.62)**	MD -1.94 (-5.54 to 1.66)	MD -0.61 (-4.73 to 3.5)	MD -2.56 (-5.71 to 0.58)	MD -0.3 (-3.3 to 2.69)	MD -2.67 (-6.39 to 1.04)
Ischaemic preconditioning	-	MD 0.41 (-3.59 to 4.4)	MD 1.73 (-2.73 to 6.19)	MD -0.22 (-3.81 to 3.37)	MD 2.04 (-1.41 to 5.49)	MD -0.33 (-4.43 to 3.76)
Antioxidants	-	-	MD 1.33 (-4.14 to 6.79)	MD -0.63 (-5.41 to 4.16)	MD 1.63 (-3.05 to 6.32)	MD -0.74 (-5.91 to 4.44)
Immunomodulators	-	-	-	MD -1.95 (-7.13 to 3.23)	MD 0.31 (-4.78 to 5.4)	MD -2.06 (-7.61 to 3.48)
Cardiovascular modulators	-	-	-	-	MD 2.26 (-2.08 to 6.6)	MD -0.11 (-4.98 to 4.76)
Steroids	-	-	-	-	-	MD -2.37 (-7.14 to 2.4)

Figure A.19: Network plot of the interventions aiming to decrease hepatic IR injury for the outcome length of hospital stay.



Footnotes: circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison.

Figure A.20: Probability of being best intervention for the outcome length of hospital stay. No class of interventions ranked best with more than 90% probability.

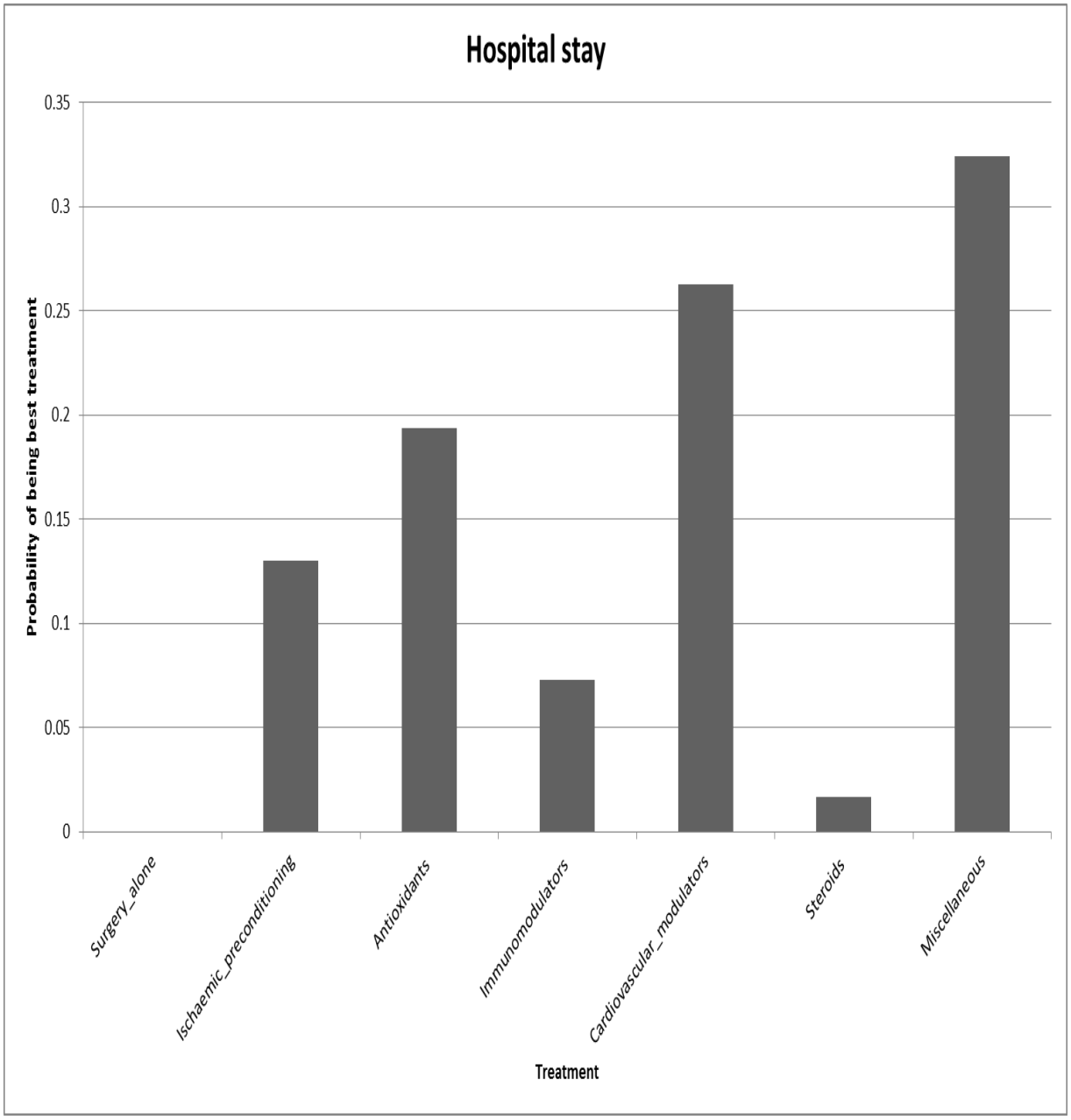
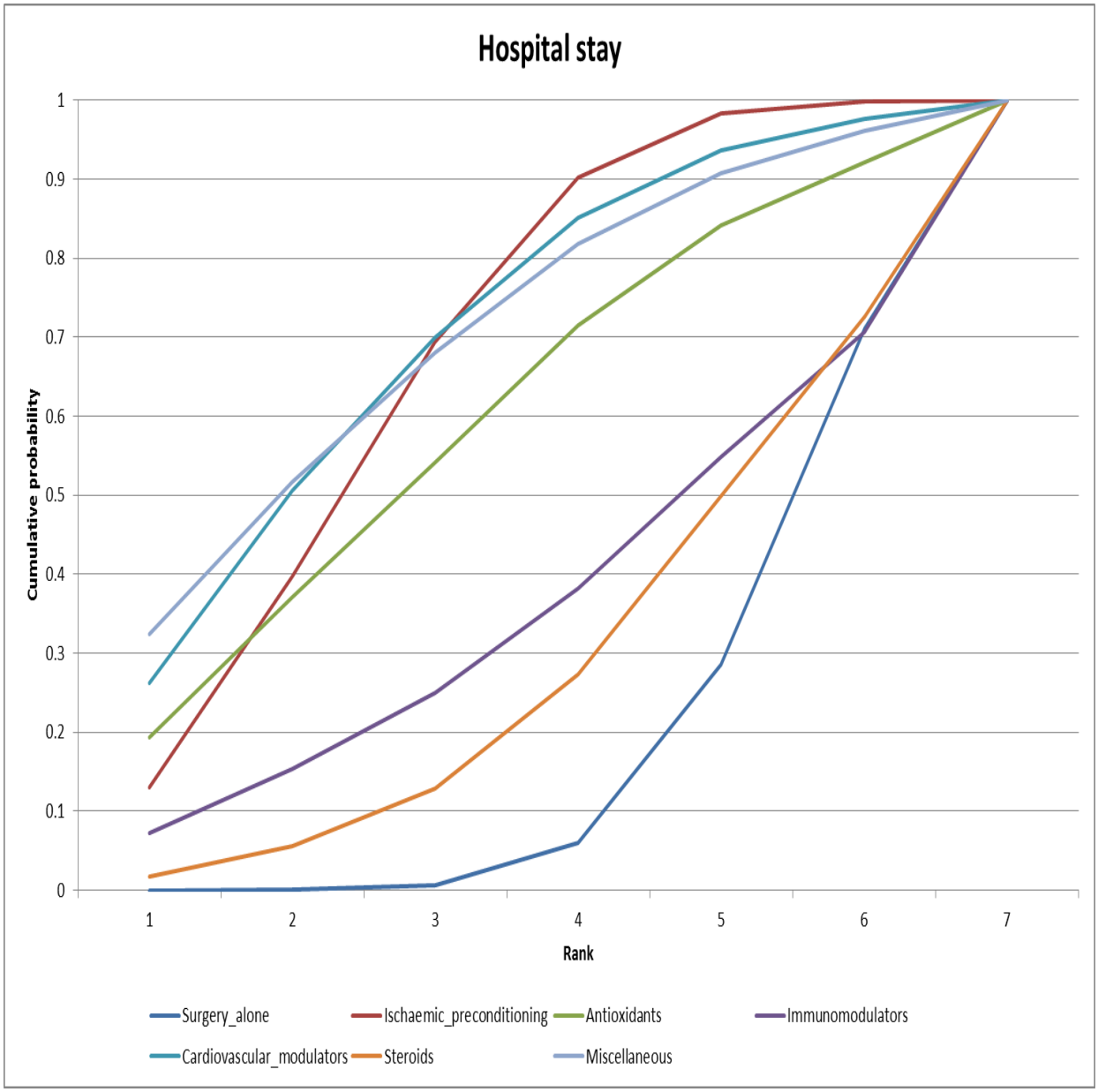


Figure A.21: Cumulative probability of ranks of different interventions aiming to decrease hepatic IR injury for the outcome length of hospital stay. There was substantial uncertainty regarding the best or worst class of interventions for this outcome.



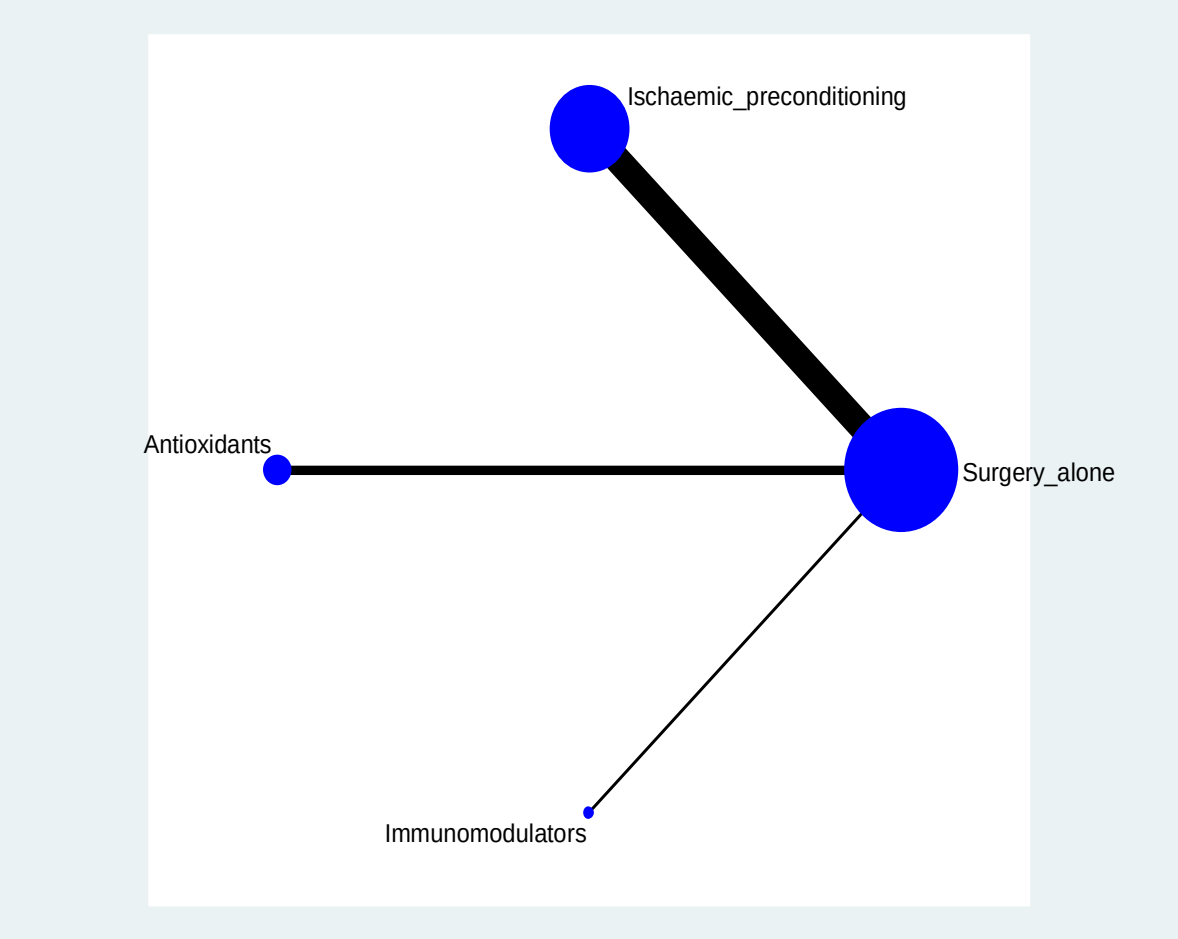
A.3.2.7. Postoperative length of ITU stay

Twelve trials (736 participants; 4 groups) provided data for the network meta-analysis on IR therapy during hepatectomy and postoperative ITU stay.[68, 76, 79, 80, 258, 317, 369, 371, 377, 381, 384, 387] The average length of ITU stay was 2 days. The random-effects model was preferred based on the DIC statistics, and there was no evidence of inconsistency. The results of the pairwise comparisons for ITU stay are provided in Table A.10. Pairwise comparison of the groups showed no evidence of any significant difference in the ITU stay. The network plot for ITU stay is shown in Figure A.22. Figures A.23 and A.24 show that none of the intervention groups ranked best or worst with more than 90% probability.

Table A.10: Pairwise mean differences (MD) of the different treatment comparisons for the outcome ITU stay (95% confidence intervals). There was no statistically significant difference between the intervention groups for the outcome ITU stay.

	Ischaemic preconditioning	**Antioxidants**	**Immunomodulators**
Surgery alone	MD -0.81 (-2.1 to 0.47)	MD -0.43 (-2.95 to 2.09)	MD -0.99 (-4.5 to 2.52)
Ischaemic preconditioning	-	MD 0.39 (-2.44 to 3.21)	MD -0.18 (-3.91 to 3.56)
Antioxidants	-	-	MD -0.56 (-4.88 to 3.75)

Figure A.22: Network plot of the interventions aiming to decrease hepatic IR injury for the outcome ITU stay.



Footnotes: circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison.

Figure A.23: Probability of being best intervention for the outcome ITU stay. None of the interventions ranked best with more than 90% probability, and there is lot of uncertainty about the intervention with the shortest ITU stay.

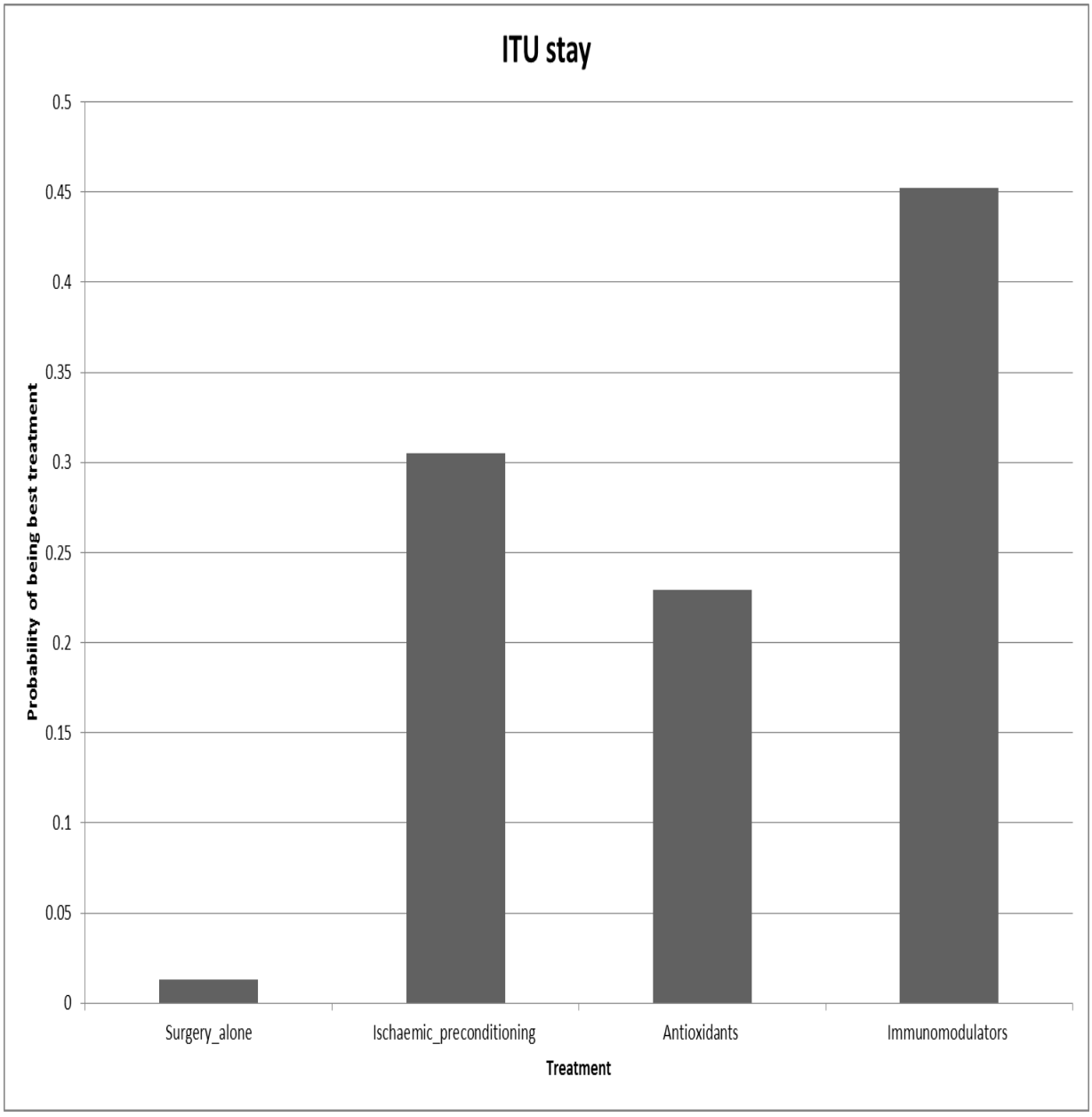
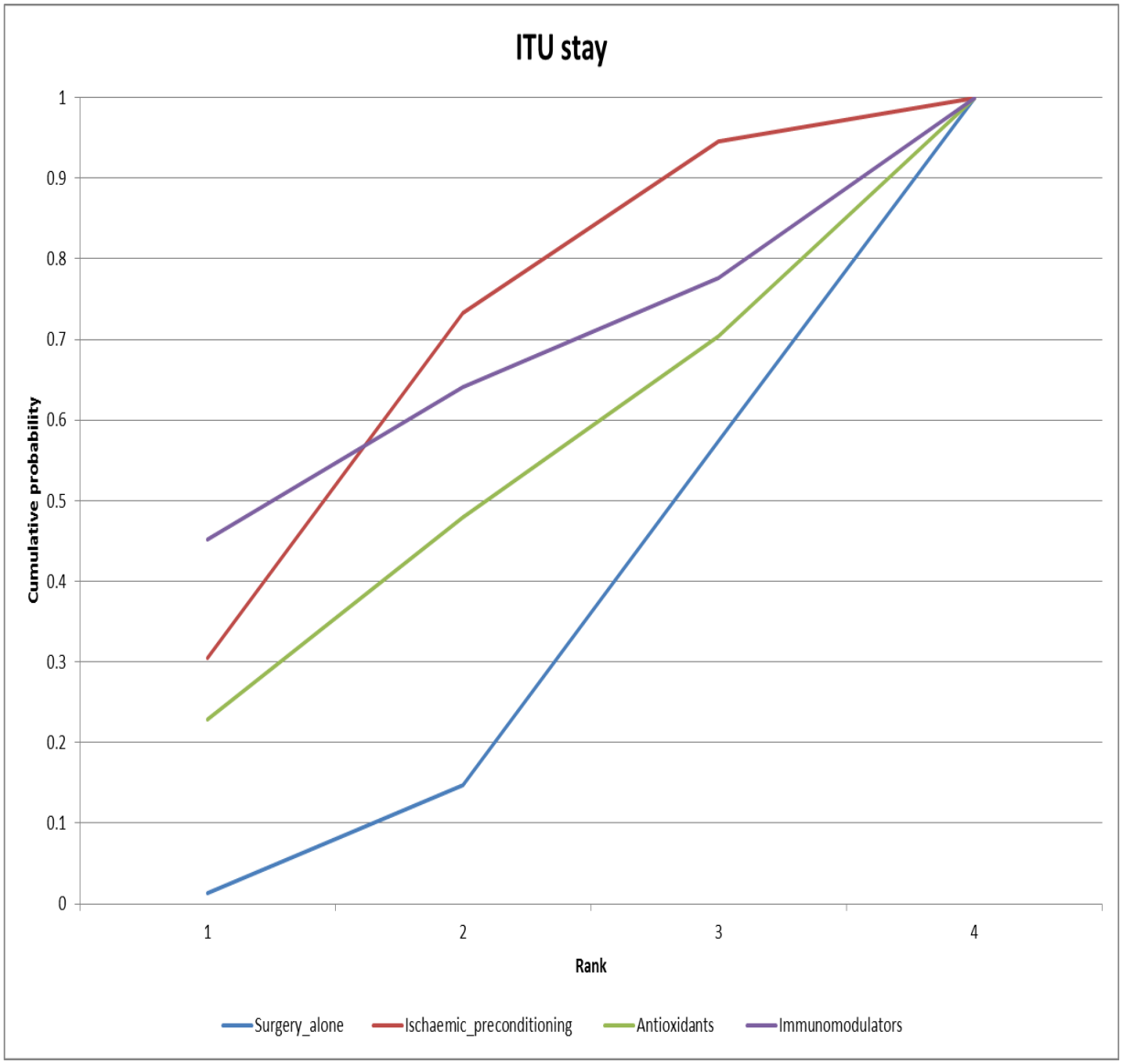


Figure A.24: Cumulative probability of ranks of different interventions aiming to decrease hepatic IR injury for the outcome ITU stay. None of the intervention groups ranked best or worst with more than 90% probability, and there was substantial uncertainty about the best or worst intervention for this outcome.



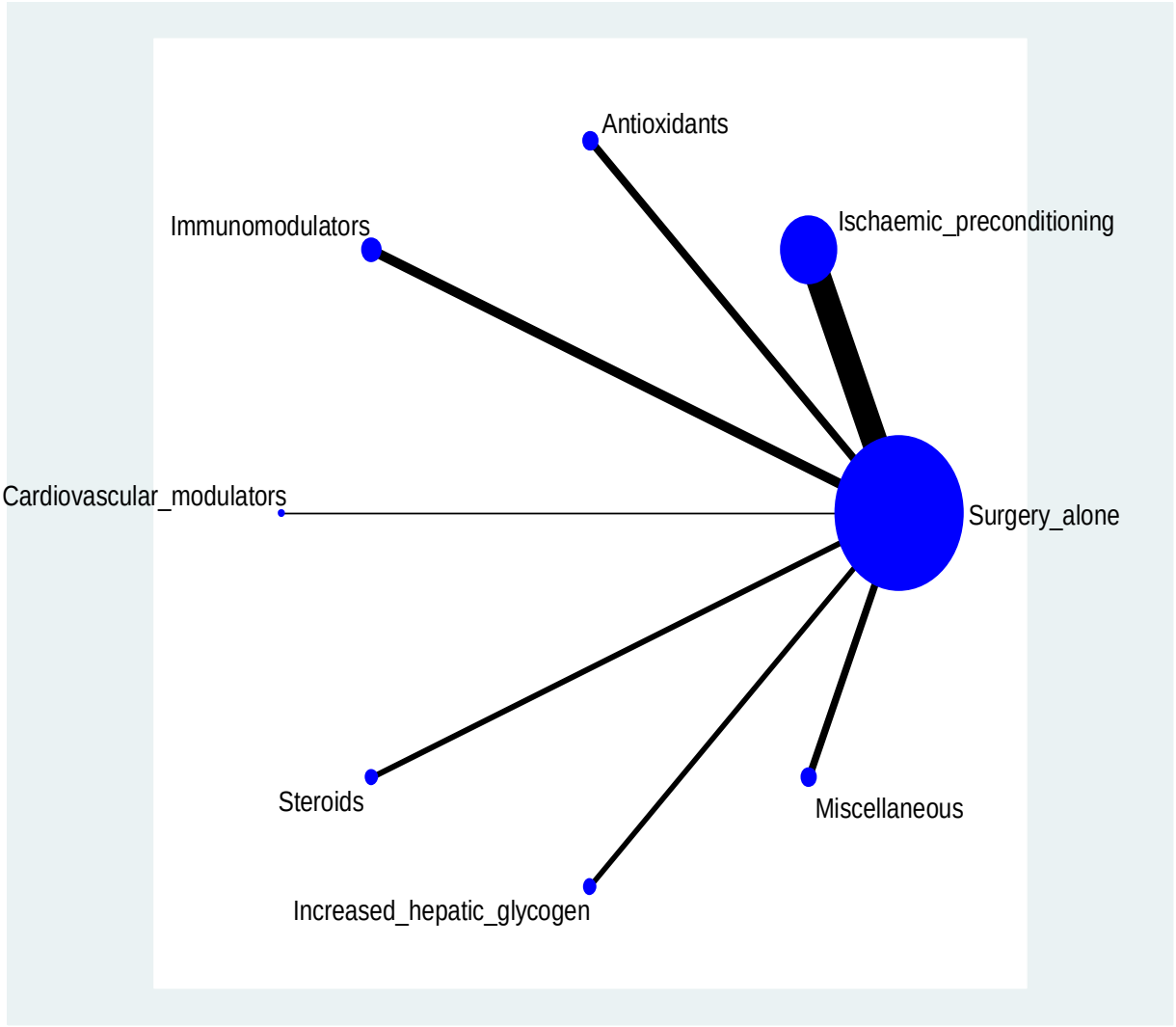
A.3.2.8. Operative time for liver resection

Thirty two trials[67, 68, 76, 79, 80, 83, 84, 86, 88, 89, 258, 317, 365-367, 369-371, 373, 374, 377-384, 389-391] (1868 participants; 8 groups) reported on operative time data included in the network meta-analysis. The fixed-effect model was preferred based on the DIC statistics, and there was no evidence of inconsistency in the networks. The results of the pairwise comparisons for operative time are provided in Table A.11. The pairwise MDs of the different treatments showed ischaemic preconditioning and increased hepatic glycogen to have significantly shorter operative time compared to steroids by 17 and 26 minutes respectively. There was no significant difference in the operating time between the other comparisons. The network plot for operative time is shown in Figure A.25. Figures A.26 and A.27 show that none of the groups ranked best or worst with more than 90% probability.

Table A.11: Pairwise mean differences (MD) of the different treatment comparisons for the outcome operative time (95% confidence intervals). Statistically significant results are in bold. The pairwise mean differences of the different treatments showed ischaemic preconditioning and increased hepatic glycogen to have significantly shorter operative time compared to steroids. There was no significant difference in the operating time between the other comparisons.

	Ischaemic preconditioning	**Antioxidants**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	MD -5.53 (-12.47 to 1.41)	MD -5.49 (-41.85 to 30.87)	MD -2.06 (-27.31 to 23.18)	MD 19.53 (-59.71 to 98.77)	MD 11.15 (-3.14 to 25.44)	MD -14.79 (-31.89 to 2.31)	MD 18.27 (-10.11 to 46.65)
Ischaemic preconditioning	-	MD 0.04 (-36.97 to 37.06)	MD 3.47 (-22.71 to 29.65)	MD 25.06 (-54.49 to 104.61)	**MD 16.68 (0.79 to 32.57)**	MD -9.26 (-27.71 to 9.19)	MD 23.8 (-5.42 to 53.02)
Antioxidants	-	-	MD 3.43 (-40.84 to 47.69)	MD 25.02 (-62.17 to 112.2)	MD 16.64 (-22.43 to 55.7)	MD -9.3 (-49.48 to 30.88)	MD 23.76 (-22.37 to 69.88)
Immunomodulators	-	-	-	MD 21.59 (-61.58 to 104.76)	MD 13.21 (-15.8 to 42.22)	MD -12.73 (-43.22 to 17.76)	MD 20.33 (-17.65 to 58.31)
Cardiovascular modulators	-	-	-	-	MD -8.38 (-88.9 to 72.14)	MD -34.32 (-115.39 to 46.75)	MD -1.26 (-85.43 to 82.91)
Steroids	-	-	-	-	-	**MD -25.94 (-48.22 to -3.66)**	MD 7.12 (-24.66 to 38.9)
Increased hepatic glycogen	-	-	-	-	-	-	MD 33.06 (-0.07 to 66.19)

Figure A.25: Network plot of the interventions aiming to decrease hepatic IR injury for the outcome operative time.



Footnotes: circles represent the intervention as a node in the network; size of circles represents the number of RCTs reporting on the intervention; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison.

Figure A.26: Probability of being best intervention for the outcome operative time. None of the interventions ranked best with more than 90% probability, and there is lot of uncertainty about the intervention with the shortest operative time.

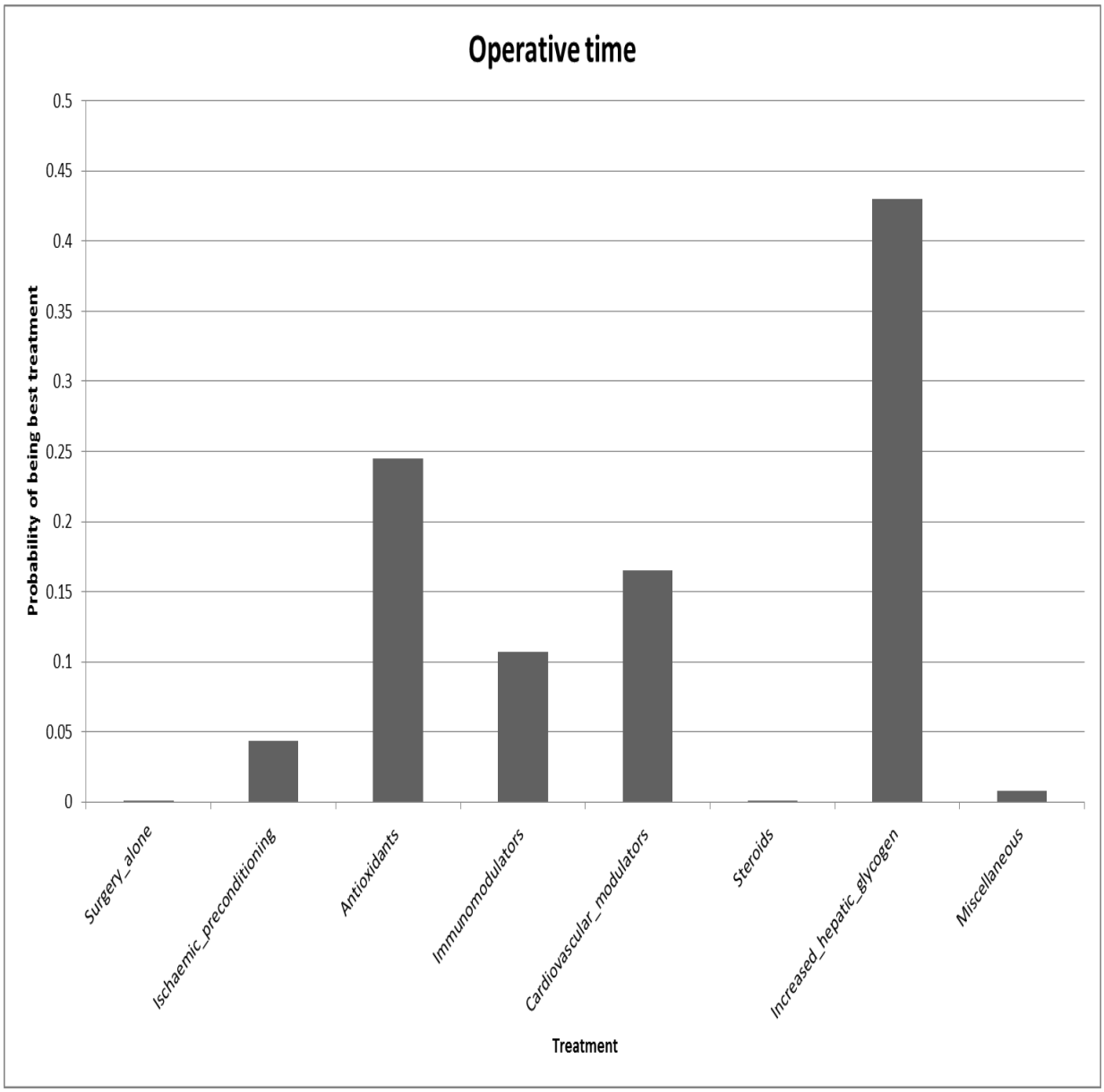
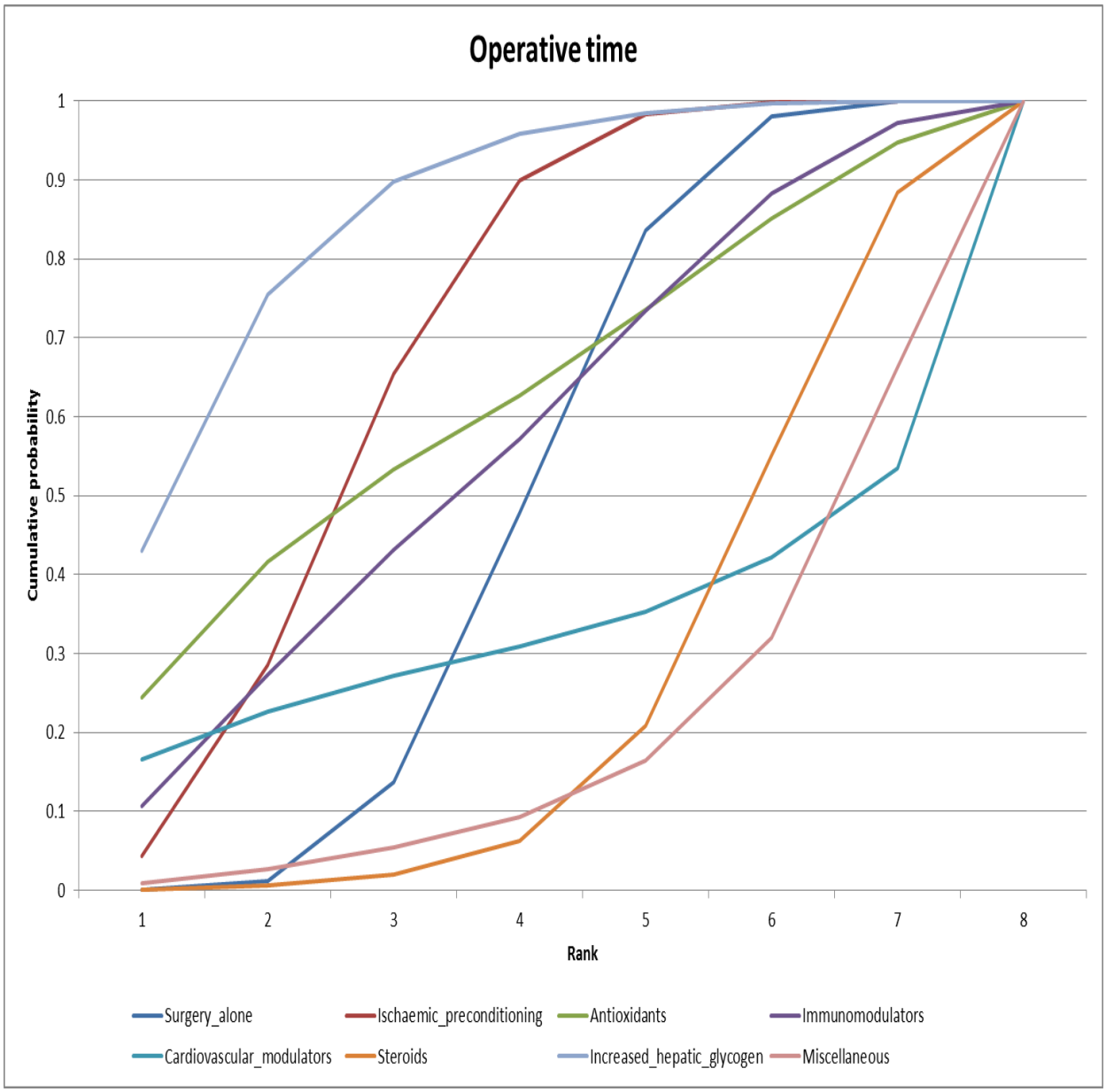


Figure A.27: Cumulative probability of ranks of different interventions aiming to decrease hepatic IR injury for the outcome operative time. None of the intervention groups ranked best or worst with more than 90% probability, and there was substantial uncertainty about the best or worst intervention for this outcome.



A.3.2.9. Summary of results of the overall network meta-analysis

The overall network meta-analysis was performed to compare eight classes of active interventions aimed at decreasing IR injury along with a control group which was surgery alone. The classes of intervention were grouped based on their mechanism of action. Figure A.28 is a rankogram showing the probability that a class of interventions is best for each outcome of interest for the overall network meta-analysis. None of the treatment groups appear clearly superior to others when all the outcomes are considered together. There does not seem to be much correlation between a treatment group being best in reducing operative blood loss and being best in reducing serious adverse events and blood transfusion. No specific weighting was given to the different outcomes. Ischaemic preconditioning did well with most outcomes and especially in reducing operative blood loss.

All statistically significant results of the pairwise comparisons during the overall network meta-analysis of the different classes of interventions for all outcomes of interest are shown in Table A.12. The classes of interventions with the highest probability of ranking from best to worst (1st to 9th) for the outcomes of interest are summarised in Table A.13.

Figure A.28: Rankogram showing the probability that a class of interventions is best treatment for each outcome of interest.

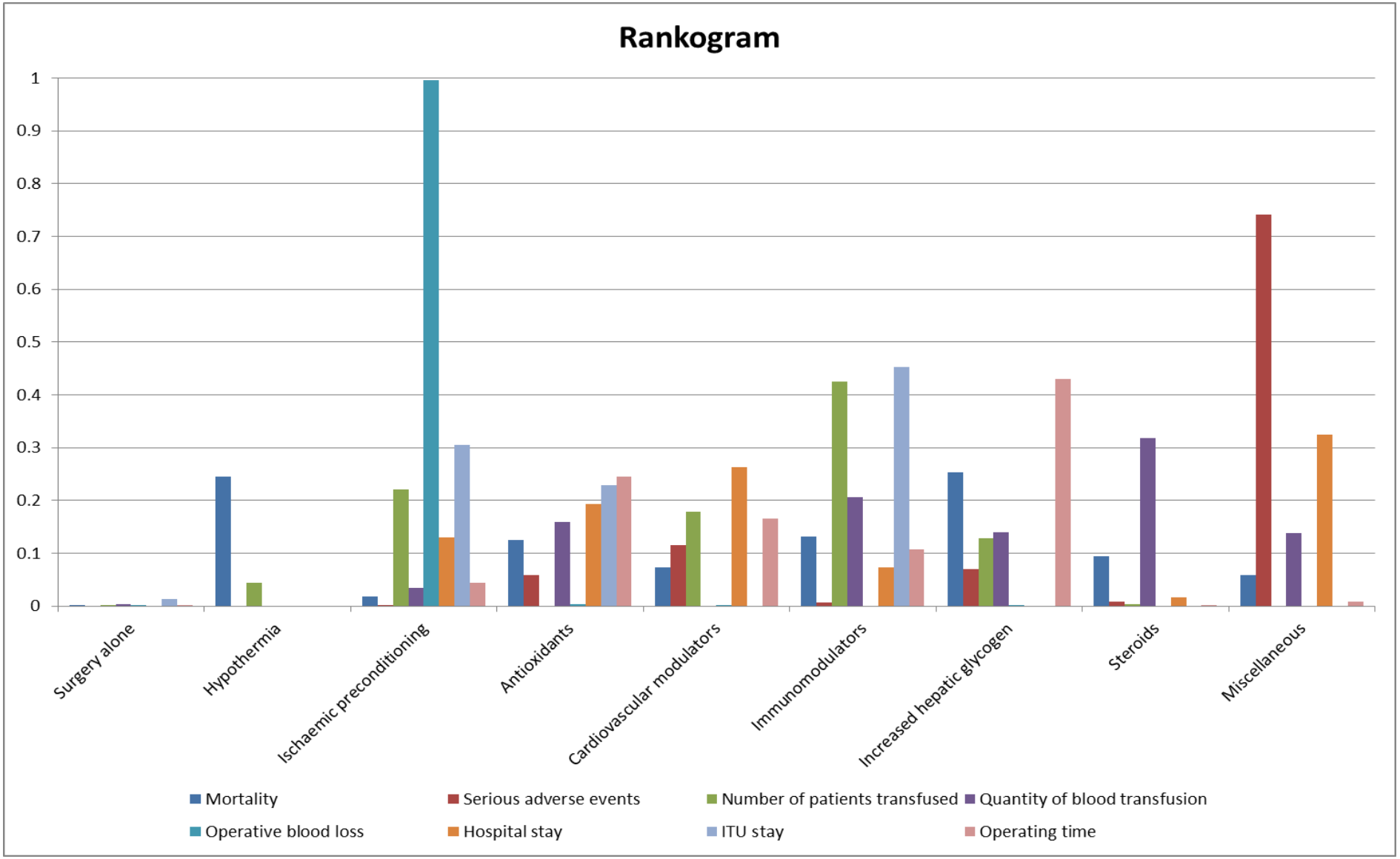


Table A.12: Statistically significant pairwise odds ratios (yellow treatment over blue treatment) and mean differences (yellow treatment minus blue treatment) of the comparisons of the classes of interventions for all outcomes of interest.

CLASSES OF INTERVENTIONS	Hypothermia	Ischaemic preconditioning	Antioxidants	Immunomodulators
Surgery alone	MD 247.1 (143.59 to 350.61)[3]	OR 0.66 (0.44- 0.98)[1] MD -35.97 (-53.76 to -18.18)[3] MD -2.34 (-4.06 to -0.62)[4]	MD 207 (34.13 to 379.87)[3]	MD 231.2 (145.82 to 316.58)[3]
Hypothermia	NA	MD -283.07 (-388.09 to -178.05)[3]	NO	NO
Ischaemic preconditioning	NA	NA	MD 242.97 (69.19 to 416.75)[3]	MD 267.17 (179.96 to 354.38)[3]
Antioxidants	NA	NA	NA	NO
	Cardiovascular modulators	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	OR 0.39 (0.18-0.87)[1] MD 142.2 (61.59 to 222.81)[3]	MD 69.32 (21.46 to 117.18)[3]	MD 92.04 (25.2 to 158.88)[3]	OR 0.21 (0.08-0.51)[1] MD 209.7 (118.32 to 301.08)[3]
Hypothermia	NO	MD -177.78 (-291.82 to -63.74)[3]	MD -155.06 (-278.27 to -31.85)[3]	NO
Ischaemic preconditioning	MD 178.17 (95.62 to 260.72)[3]	OR 2.31 (1.03-5.18)[2] MD 105.29 (54.23 to 156.35)[3] MD 16.68 (0.79 to 32.57)[5]	MD 128.01 (58.85 to 197.17)[3]	OR 0.31 (0.12-0.85)[1] MD 245.67 (152.58 to 338.76)[3]
Antioxidants	NO	NO	NO	NO
Immuno-modulators	NO	MD -161.88 (-259.76 to -64)[3]	MD -139.16 (-247.59 to -30.73)[3]	OR 0.31 (0.1-0.96)[1]
Cardiovascular modulators	NA	NO	NO	NO

Table 7.20 continued				
Steroids	NA	NA	MD -25.94 (-48.22 to -3.66)[5]	OR 0.31 (0.1-0.99)[1] MD 140.38 (37.23 to 243.53)[3]
Increased hepatic glycogen	NA	NA	NA	MD 117.66 (4.45 to 230.87)[3]

Footnotes: OR=odds ratio; MD=mean difference; (95% credible intervals); NA=not applicable; NO=no statistically significant outcomes for this pairwise comparison; 1=serious adverse events; 2=proportion of patients transfused, 3=operative blood loss, 4=length of hospital stay, 5=operative time. There was no statistically significant difference between the interventions for the outcomes: mortality, quantity of blood transfusion per patient, and ITU stay.

Table A.13: Classes of interventions aiming to decrease hepatic IR injury with the highest probability of ranking from best to worst (1st to 9th) for the outcomes of interest.

OUTCOMES	RANKS								
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Mortality	Increased hepatic glycogen P=0.253	Immuno-modulators P=0.225	Immuno-modulators P=0.212	Ischaemic preconditioning P=0.205	Surgery alone P=0.231	Surgery alone P=0.290	Surgery alone P=0.221	Steroids P=0.179	Hypothermia P=0.292
Serious adverse events	Miscellaneous P=0.742	Cardiovascular modulators P=0.374	Cardiovascular modulators P=0.246	Ischaemic preconditioning P=0.226	Ischaemic preconditioning P=0.293	Ischaemic preconditioning P=0.235	Surgery alone P=0.404	Surgery alone P=0.455	NA 1
Proportion of patients transfused	Immuno-modulators P=0.424	Ischaemic preconditioning P=0.395	Ischaemic preconditioning P=0.272	Surgery alone P=0.404	Surgery alone P=0.280	Steroids P=0.477	Hypothermia P=0.665	NA 2	NA
Quantity of blood transfusion	Steroids P=0.318	Antioxidants P=0.226	Antioxidants P=0.198	Surgery alone P=0.282	Surgery alone P=0.317	Surgery alone P=0.179	Miscellaneous P=0.255	NA 3	NA
Operative blood loss	Ischaemic preconditioning P=0.997	Surgery alone P=0.985	Steroids P=0.451	Increased hepatic glycogen P=0.492	Cardiovascular modulators P=0.478	Miscellaneous P=0.256	Miscellaneous P=0.296	Immuno-modulators P=0.316	Hypothermia P=0.388
Length of hospital stay	Miscellaneous P=0.324	Ischaemic preconditioning P=0.268	Ischaemic preconditioning P=0.297	Ischaemic preconditioning P=0.208	Surgery alone P=0.226	Surgery alone P=0.425	Immuno-modulators P=0.294	NA 4	NA
ITU stay	Immuno-modulators P=0.453	Ischaemic preconditioning P=0.427	Surgery alone P=0.427	Surgery alone P=0.426	NA 5	NA	NA	NA	NA
Operating time	Increased hepatic glycogen P=0.430	Increased hepatic glycogen P=0.324	Ischaemic preconditioning P=0.369	Surgery alone P=0.341	Surgery alone P=0.358	Steroids P=0.343	Miscellaneous P=0.343	Cardiovascular modulators P=0.465	NA 6

Footnotes: P=probability of ranking; NA=not applicable because less than 9 interventions were analysed for this outcome. Interventions not included in the analysis for this outcome: 1=hypothermia; 2=antioxidants, miscellaneous; 3=hypothermia, cardiovascular modulators; 4=hypothermia, increased hepatic glycogen; 5=hypothermia, cardiovascular modulators, steroids, increased hepatic glycogen, miscellaneous, 6=hypothermia.

A.3.3. Sensitivity network meta-analysis – individual interventions

A network meta-analysis was performed to compare the individual interventions included in each class of interventions aimed at decreasing IR injury during major liver resection surgery (Table 7.3). No significant difference was found in mortality, quantity of blood transfusion per patient, and ITU stay, between the different interventions aimed at reducing IR injury. As there is no direct measure of IR injury multiple clinical end points were measured which are likely to reflect the benefits or harms of a group of interventions aimed at reducing IR injury. Pairwise comparisons showed fewer people transfused with ischaemic preconditioning compared to steroids, as shown in Table A.14. Furthermore, ischaemic preconditioning was found to have significantly lower operative blood loss compared to surgery alone, hypothermia, prostaglandin E1, steroids, verapamil, S-adenosyl-L-methionine, pre-storing hepatocellular glycogen, insulin, sivelestat, branched chain aminoacids, gabexate mesilate, and melatonin. Surgery alone had significantly lower operative blood loss compared to hypothermia, prostaglandin E1, steroids, verapamil, S-adenosyl-L-methionine, insulin, branched chain aminoacids, gabexate mesilate, and melatonin. The pairwise comparisons for operative blood loss are shown in Table A.15 Part A and Part B.

Ischaemic preconditioning was found to have significantly fewer serious adverse events compared to surgery alone. Sevoflurane was found to have significantly fewer serious adverse events compared to surgery alone, ischaemic preconditioning, steroids, and pentoxifylline. Both verapamil and gabexate mesilate had significantly fewer serious adverse events compared to surgery alone and pentoxifylline. The pairwise comparisons for serious adverse events are shown in Table A.16 Part A and Part B.

Ischaemic preconditioning was found to have significantly shorter hospital stay compared to surgery alone. Furthermore, ischaemic preconditioning and pre-storing hepatocellular glycogen were found to have significantly shorter operative time compared to steroids; and vitamin E was found to have shorter operative time compared to branched chain amino acids.

Table A.14: Sensitivity analysis – individual interventions. Pairwise odds ratios (OR) of the different treatment comparisons for the outcome proportion of patients transfused (95% confidence intervals). Statistically significant results are in bold. Pairwise comparisons showed fewer people transfused with ischaemic preconditioning compared to steroids. There was no significant difference in the proportion of patients transfused between the other comparisons.

	Hypothermia	**Ischaemic preconditioning**	**Steroid**	**Verapamil**	**Insulin**	**Pentoxifylline**
Surgery alone	OR 3.18 (0.35 to 28.65)	OR 0.71 (0.5 to 1.01)	OR 1.63 (0.78 to 3.38)	OR 0.84 (0.35 to 2.01)	OR 1.02 (0.35 to 3.02)	OR 0.65 (0.18 to 2.31)
Hypothermia	-	OR 0.22 (0.02 to 2.06)	OR 0.51 (0.05 to 5.2)	OR 0.26 (0.02 to 2.82)	OR 0.32 (0.03 to 3.73)	OR 0.2 (0.02 to 2.58)
Ischaemic preconditioning	-	-	**OR 2.3 (1.02 to 5.19)**	OR 1.19 (0.46 to 3.05)	OR 1.45 (0.46 to 4.52)	OR 0.91 (0.24 to 3.43)
Steroid	-	-	-	OR 0.52 (0.16 to 1.62)	OR 0.63 (0.17 to 2.32)	OR 0.4 (0.09 to 1.73)
Verapamil	-	-	-	-	OR 1.22 (0.3 to 4.91)	OR 0.77 (0.16 to 3.62)
Insulin	-	-	-	-	-	OR 0.63 (0.12 to 3.35)

Table A.15 Part A: Sensitivity analysis – individual interventions. Pairwise mean differences (MD) of the different treatment comparisons for the outcome operative blood loss (95% confidence intervals). Statistically significant results are in bold. Ischaemic preconditioning was found to have significantly lower operative blood loss compared to surgery alone, hypothermia, prostaglandin E1, steroids, verapamil, S-adenosyl-L-methionine, pre-storing hepatocellular glycogen, insulin, sivelestat, branched chain aminoacids, gabexate mesilate, and melatonin. Surgery alone had significantly lower operative blood loss compared to hypothermia, prostaglandin E1, steroids, verapamil, S-adenosyl-L-methionine, insulin, branched chain aminoacids, gabexate mesilate, and melatonin.

	Hypothermia	**Ischaemic preconditioning**	**Sevoflurane**	**Prostaglandin E1**	**Amrinone**	**Steroids**	**Ulinastatin**	**Verapamil**	**S-adenosyl-L-methionine**
Surgery alone	**MD 245.9 (142.35 to 349.45)**	**MD -36 (-53.42 to -18.58)**	MD 69.59 (-61.95 to 201.13)	**MD 163.5 (34.04 to 292.96)**	MD 101.3 (-58.85 to 261.45)	**MD 69.54 (21.79 to 117.29)**	MD 92.46 (-43.31 to 228.23)	**MD 111 (26.41 to 195.59)**	**MD 174.4 (25.69 to 323.11)**
Hypothermia	-	**MD -281.9 (-386.9 to -176.9)**	MD -176.31 (-343.71 to -8.91)	MD -82.4 (-248.17 to 83.37)	MD -144.6 (-335.31 to 46.11)	MD -176.36 (-290.38 to -62.34)	MD -153.44 (-324.19 to 17.31)	MD -134.9 (-268.61 to -1.19)	MD -71.5 (-252.7 to 109.7)
Ischaemic preconditioning	-	-	MD 105.59 (-27.09 to 238.27)	**MD 199.5 (68.88 to 330.12)**	MD 137.3 (-23.8 to 298.4)	**MD 105.54 (54.72 to 156.36)**	MD 128.46 (-8.42 to 265.34)	**MD 147 (60.63 to 233.37)**	**MD 210.4 (60.68 to 360.12)**
Sevoflurane	-	-	-	MD 93.91 (-90.65 to 278.47)	MD 31.71 (-175.53 to 238.95)	MD -0.05 (-139.98 to 139.88)	MD 22.87 (-166.17 to 211.91)	MD 41.41 (-114.98 to 197.8)	MD 104.81 (-93.72 to 303.34)
Prostaglandin E1	-	-	-	-	MD -62.2 (-268.13 to 143.73)	MD -93.96 (-231.94 to 44.02)	MD -71.04 (-258.64 to 116.56)	MD -52.5 (-207.15 to 102.15)	MD 10.9 (-186.26 to 208.06)
Amrinone	-	-	-	-	-	MD -31.76 (-198.88 to 135.36)	MD -8.84 (-218.8 to 201.12)	MD 9.7 (-171.42 to 190.82)	MD 73.1 (-145.44 to 291.64)
Steroids	-	-	-	-	-	-	MD 22.92 (-121 to 166.84)	MD 41.46 (-55.68 to 138.6)	MD 104.86 (-51.32 to 261.04)
Ulinastatin	-	-	-	-	-	-	-	MD 18.54 (-141.43 to 178.51)	MD 81.94 (-119.42 to 283.3)
Verapamil	-	-	-	-	-	-	-	-	MD 63.4 (-107.68 to 234.48)

Table A.15 Part B: Sensitivity analysis – individual interventions. Pairwise mean differences (MD) of the different treatment comparisons for the outcome operative blood loss (95% confidence intervals). Statistically significant results are in bold. Ischaemic preconditioning was found to have significantly lower operative blood loss compared to surgery alone, hypothermia, prostaglandin E1, steroids, verapamil, S-adenosyl-L-methionine, pre-storing hepatocellular glycogen, insulin, sivelestat, branched chain aminoacids, gabexate mesilate, and melatonin. Surgery alone had significantly lower operative blood loss compared to hypothermia, prostaglandin E1, steroids, verapamil, S-adenosyl-L-methionine, insulin, branched chain aminoacids, gabexate mesilate, and melatonin.

	Pre-storing hepatocellular glycogen	**Allopurinol**	**Insulin**	**Sivelestat**	**Branched chain amino acids**	**OKY046**	**Gabexate mesilate**	**Melatonin**	**Pentoxifylline**
Surgery alone	MD 61.54 (-7.57 to 130.65)	MD 37.71 (-155.31 to 230.73)	**MD 194.8 (35.22 to 354.38)**	MD 147 (-5.92 to 299.92)	**MD 203.2 (45.36 to 361.04)**	MD 75.47 (-117.35 to 268.29)	**MD 190.9 (64.79 to 317.01)**	**MD 180.4 (5.72 to 355.08)**	MD 73.39 (-66.08 to 212.86)
Hypothermia	MD -184.36 (-308.85 to -59.87)	MD -208.19 (-427.23 to 10.85)	MD -51.1 (-241.33 to 139.13)	MD -98.9 (-283.58 to 85.78)	MD -42.7 (-231.47 to 146.07)	MD -170.43 (-389.3 to 48.44)	MD -55 (-218.17 to 108.17)	MD -65.5 (-268.56 to 137.56)	MD -172.51 (-346.22 to 1.2)
Ischaemic preconditioning	**MD 97.54 (26.27 to 168.81)**	MD 73.71 (-120.1 to 267.52)	**MD 230.8 (70.27 to 391.33)**	**MD 183 (29.09 to 336.91)**	**MD 239.2 (80.4 to 398)**	MD 111.47 (-82.14 to 305.08)	**MD 226.9 (99.6 to 354.2)**	**MD 216.4 (40.86 to 391.94)**	MD 109.39 (-31.17 to 249.95)
Sevoflurane	MD -8.05 (-156.64 to 140.54)	MD -31.88 (-265.46 to 201.7)	MD 125.21 (-81.6 to 332.02)	MD 77.41 (-124.3 to 279.12)	MD 133.61 (-71.85 to 339.07)	MD 5.88 (-227.54 to 239.3)	MD 121.31 (-60.91 to 303.53)	MD 110.81 (-107.85 to 329.47)	MD 3.8 (-187.91 to 195.51)
Prostaglandin E1	MD -101.96 (-248.71 to 44.79)	MD -125.79 (-358.2 to 106.62)	MD 31.3 (-174.19 to 236.79)	MD -16.5 (-216.86 to 183.86)	MD 39.7 (-164.44 to 243.84)	MD -88.03 (-320.28 to 144.22)	MD 27.4 (-153.33 to 208.13)	MD 16.9 (-200.52 to 234.32)	MD -90.11 (-280.41 to 100.19)
Amrinone	MD -39.76 (-214.19 to 134.67)	MD -63.59 (-314.4 to 187.22)	MD 93.5 (-132.59 to 319.59)	MD 45.7 (-175.73 to 267.13)	MD 101.9 (-122.96 to 326.76)	MD -25.83 (-276.49 to 224.83)	MD 89.6 (-114.24 to 293.44)	MD 79.1 (-157.88 to 316.08)	MD -27.91 (-240.28 to 184.46)
Steroids	MD -8 (-92 to 76)	MD -31.83 (-230.67 to 167.01)	MD 125.26 (-41.31 to 291.83)	MD 77.46 (-82.74 to 237.66)	MD 133.66 (-31.24 to 298.56)	MD 5.93 (-192.72 to 204.58)	MD 121.36 (-13.48 to 256.2)	MD 110.86 (-70.22 to 291.94)	MD 3.85 (-143.57 to 151.27)
Ulinastatin	MD -30.92 (-183.27 to 121.43)	MD -54.75 (-290.74 to 181.24)	MD 102.34 (-107.18 to 311.86)	MD 54.54 (-149.95 to 259.03)	MD 110.74 (-97.46 to 318.94)	MD -16.99 (-252.82 to 218.84)	MD 98.44 (-86.86 to 283.74)	MD 87.94 (-133.29 to 309.17)	MD -19.07 (-213.71 to 175.57)

Table A.15 Part B continued									
Verapamil	MD -49.46 (-158.69 to 59.77)	MD -73.29 (-284.03 to 137.45)	MD 83.8 (-96.82 to 264.42)	MD 36 (-138.76 to 210.76)	MD 92.2 (-86.88 to 271.28)	MD -35.53 (-246.09 to 175.03)	MD 79.9 (-71.95 to 231.75)	MD 69.4 (-124.68 to 263.48)	MD -37.61 (-200.73 to 125.51)
S-adenosyl-L-methionine	MD -112.86 (-276.84 to 51.12)	MD -136.69 (-380.35 to 106.97)	MD 20.4 (-197.73 to 238.53)	MD -27.4 (-240.7 to 185.9)	MD 28.8 (-188.06 to 245.66)	MD -98.93 (-342.43 to 144.57)	MD 16.5 (-178.48 to 211.48)	MD 6 (-223.4 to 235.4)	MD -101.01 (-304.89 to 102.87)
Pre-storing hepatocellular glycogen	-	MD -23.83 (-228.85 to 181.19)	MD 133.26 (-40.64 to 307.16)	MD 85.46 (-82.35 to 253.27)	MD 141.66 (-30.65 to 313.97)	MD 13.93 (-190.91 to 218.77)	MD 129.36 (-14.44 to 273.16)	MD 118.86 (-68.99 to 306.71)	MD 11.85 (-143.81 to 167.51)
Allopurinol	-	-	MD 157.09 (-93.36 to 407.54)	MD 109.29 (-136.96 to 355.54)	MD 165.49 (-83.85 to 414.83)	MD 37.76 (-235.07 to 310.59)	MD 153.19 (-77.37 to 383.75)	MD 142.69 (-117.63 to 403.01)	MD 35.68 (-202.46 to 273.82)
Insulin	-	-	-	MD -47.8 (-268.82 to 173.22)	MD 8.4 (-216.05 to 232.85)	MD -119.33 (-369.63 to 130.97)	MD -3.9 (-207.3 to 199.5)	MD -14.4 (-251 to 222.2)	MD -121.41 (-333.35 to 90.53)
Sivelestat	-	-	-	-	MD 56.2 (-163.57 to 275.97)	MD -71.53 (-317.63 to 174.57)	MD 43.9 (-154.31 to 242.11)	MD 33.4 (-198.75 to 265.55)	MD -73.61 (-280.58 to 133.36)
Branched chain amino acids	-	-	-	-	-	MD -127.73 (-376.92 to 121.46)	MD -12.3 (-214.33 to 189.73)	MD -22.8 (-258.22 to 212.62)	MD -129.81 (-340.44 to 80.82)
OKY 046	-	-	-	-	-	-	MD 115.43 (-114.97 to 345.83)	MD 104.93 (-155.25 to 365.11)	MD -2.08 (-240.06 to 235.9)
Gabexate mesilate	-	-	-	-	-	-	-	MD -10.5 (-225.94 to 204.94)	MD -117.51 (-305.54 to 70.52)
Melatonin	-	-	-	-	-	-	-	-	MD -107.01 (-330.54 to 116.52)

Table A.16 Part A: Sensitivity analysis – individual interventions. Pairwise odds ratios (OR) of the different treatment comparisons for the outcome serious adverse events (95% confidence intervals). Statistically significant results are in bold. Ischaemic preconditioning was found to have significantly fewer serious adverse events compared to surgery alone. Sevoflurane was found to have significantly fewer serious adverse events compared to surgery alone, ischaemic preconditioning, steroids, and pentoxifylline. Both verapamil and gabexate mesilate had significantly fewer serious adverse events compared to surgery alone and pentoxifylline.

	Ischaemic preconditioning	**Vitamin E**	**Sevoflurane**	**Prostaglandin E1**	**Steroids**	**Ulinastatin**	**Verapamil**	**Antioxidant multivitamin**
Surgery alone	**OR 0.65 (0.44 to 0.97)**	OR 0.77 (0.18 to 3.28)	**OR 0.17 (0.06 to 0.48)**	OR 1.02 (0 to 503.71)	OR 0.66 (0.32 to 1.34)	OR 0.34 (0.04 to 2.62)	**OR 0.35 (0.14 to 0.88)**	OR 0.06 (0 to 6.48)
Ischaemic preconditioning	-	OR 1.17 (0.26 to 5.3)	**OR 0.25 (0.08 to 0.8)**	OR 1.56 (0 to 781.64)	OR 1.01 (0.44 to 2.29)	OR 0.51 (0.06 to 4.17)	OR 0.53 (0.19 to 1.47)	OR 0.1 (0 to 10.1)
Vitamin E	-	-	OR 0.22 (0.04 to 1.32)	OR 1.33 (0 to 778.57)	OR 0.86 (0.17 to 4.34)	OR 0.44 (0.04 to 5.43)	OR 0.45 (0.08 to 2.56)	OR 0.08 (0 to 10.58)
Sevoflurane	-	-	-	OR 6.13 (0.01 to 3325.48)	**OR 3.96 (1.09 to 14.33)**	OR 2.02 (0.2 to 20.48)	OR 2.09 (CI 0.51 to 8.66)	OR 0.38 (0 to 44.1)
Prostaglandin E1	-	-	-	-	OR 0.65 (0 to 333.59)	OR 0.33 (0 to 227.66)	OR 0.34 (0 to 181.42)	OR 0.06 (0 to 143.58)
Steroids	-	-	-	-	-	OR 0.51 (0.06 to 4.5)	OR 0.53 (0.16 to 1.72)	OR 0.1 (0 to 10.42)
Ulinastatin	-	-	-	-	-	-	OR 1.03 (0.11 to 9.88)	OR 0.19 (0 to 29.86)
Verapamil	-	-	-	-	-	-	-	OR 0.18 (0 to 20.5)

Table A.16 Part B: Sensitivity analysis – individual interventions. Pairwise odds ratios (OR) of the different treatment comparisons for the outcome serious adverse events (95% confidence intervals). Statistically significant results are in bold. Ischaemic preconditioning was found to have significantly fewer serious adverse events compared to surgery alone. Sevoflurane was found to have significantly fewer serious adverse events compared to surgery alone, ischaemic preconditioning, steroids, and pentoxifylline. Both verapamil and gabexate mesilate had significantly fewer serious adverse events compared to surgery alone and pentoxifylline.

	Trimetazidine	**Insulin**	**Branched chain amino acids**	**Gabexate mesilate**	**Melatonin**	**Pentoxifylline**
Surgery alone	OR 0.53 (0.11 to 2.63)	OR 0.69 (0.15 to 3.09)	OR 0.15 (0 to 17.94)	**OR 0.21 (0.06 to 0.73)**	OR 0.48 (0.09 to 2.66)	OR 1.34 (0.54 to 3.35)
Ischaemic preconditioning	OR 0.81 (0.15 to 4.24)	OR 1.05 (0.22 to 4.99)	OR 0.23 (0 to 27.95)	OR 0.32 (0.09 to 1.2)	OR 0.74 (0.13 to 4.26)	OR 2.05 (0.76 to 5.58)
Vitamin E	OR 0.69 (0.08 to 6.02)	OR 0.9 (0.11 to 7.27)	OR 0.19 (0 to 29.08)	OR 0.27 (0.04 to 1.87)	OR 0.63 (0.07 to 5.93)	OR 1.75 (0.31 to 9.76)
Sevoflurane	OR 3.18 (0.46 to 21.91)	OR 4.13 (0.65 to 26.2)	OR 0.89 (0.01 to 121.59)	OR 1.26 (0.24 to 6.56)	OR 2.91 (0.39 to 21.76)	**OR 8.07 (1.98 to 33)**
Prostaglandin E1	OR 0.52 (0 to 315.31)	OR 0.67 (0 to 400.1)	OR 0.15 (0 to 371.05)	OR 0.21 (0 to 115.63)	OR 0.47 (0 to 296.08)	OR 1.32 (0 to 698.36)
Steroids	OR 0.8 (0.14 to 4.67)	OR 1.04 (0.2 to 5.53)	OR 0.23 (0 to 28.8)	OR 0.32 (0.08 to 1.35)	OR 0.73 (0.12 to 4.67)	OR 2.04 (0.64 to 6.53)
Ulinastatin	OR 1.57 (0.12 to 21.34)	OR 2.04 (0.16 to 26.1)	OR 0.44 (0 to 81.47)	OR 0.62 (0.06 to 6.92)	OR 1.44 (0.1 to 20.77)	OR 3.99 (0.42 to 37.86)
Verapamil	OR 1.52 (0.24 to 9.76)	OR 1.98 (0.34 to 11.64)	OR 0.43 (0 to 56.57)	OR 0.6 (0.13 to 2.88)	OR 1.39 (0.2 to 9.72)	**OR 3.86 (1.04 to 14.3)**
Antioxidant multivitamin	OR 8.29 (0.06 to 1107.87)	OR 10.78 (0.08 to 1394.97)	OR 2.33 (0 to 1821.3)	OR 3.29 (0.03 to 396.21)	OR 7.59 (0.05 to 1048.3)	OR 21.07 (0.19 to 2347.95)
Trimetazidine	-	OR 1.3 (0.14 to 11.78)	OR 0.28 (0 to 44.24)	OR 0.4 (0.05 to 3.05)	OR 0.92 (0.09 to 9.54)	OR 2.54 (0.4 to 16.18)

Table A.16 Part B continued						
Insulin	-	-	OR 0.22 (0 to 32.96)	OR 0.31 (0.04 to 2.17)	OR 0.7 (0.07 to 6.85)	OR 1.95 (0.34 to 11.4)
Branched chain amino acids	-	-	-	OR 1.41 (0.01 to 201.64)	OR 3.26 (0.02 to 531.1)	OR 9.06 (0.07 to 1198.14)
Gabexate mesilate	-	-	-	-	OR 2.31 (0.28 to 19.16)	**OR 6.4 (1.35 to 30.29)**
Melatonin	-	-	-	-	-	OR 2.78 (0.4 to 19.23)

A.3.4. Sensitivity network meta-analysis – larger groups

A network meta-analysis was performed to compare the following 4 larger groups: surgery alone, hypothermia, ischaemic preconditioning, and all pharmacological interventions (Table A.3). There was no significant difference in mortality, proportion of patients transfused, quantity of blood transfusion per patient, ITU stay, and operative time, between the 4 groups. Ischaemic preconditioning was found to have a high probability (87%) of being the best treatment for operating time (Figure A.29).

Ischaemic preconditioning and pharmacological interventions were found to have significantly fewer serious adverse events compared to surgery alone. The pairwise comparisons for serious adverse events are shown in Table A.17. Pharmacological interventions had 86% probability of being the best treatment for serious adverse events. Ischaemic preconditioning had significantly lower operative blood loss compared to surgery alone, hypothermia, and pharmacological interventions, and was confirmed best treatment for operative blood loss with 100% probability. In addition, hypothermia and pharmacological interventions had significantly higher operative blood loss compared to surgery alone. The pairwise comparisons for operative blood loss are shown in Table A.18, and the probability of being best treatment is shown in Figure A.30.

Furthermore, ischaemic preconditioning and pharmacological interventions had significantly shorter hospital stay compared to surgery alone. Figure A.31 is a rankogram showing the probability that a group of treatments is best for each outcome of this sensitivity network meta-analysis. Ischaemic preconditioning did well with most outcomes and especially in reducing operative blood loss.

Figure A.29: Sensitivity analysis – larger groups. Probability of being best treatment for the outcome operating time. Ischaemic preconditioning was found to have a high probability (87%) of being the best treatment for operating time

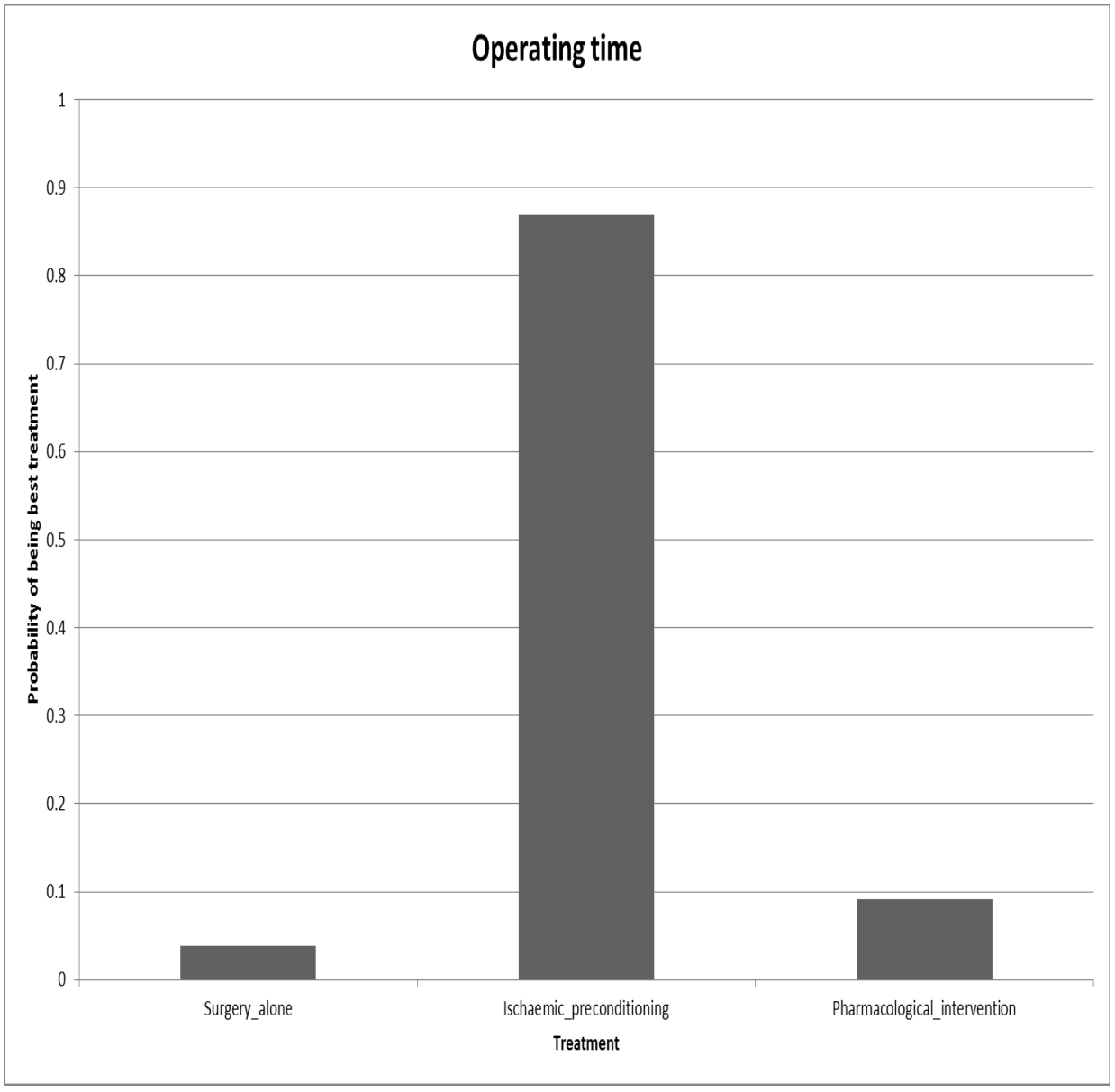


Table A.17: Sensitivity analysis – larger groups. Pairwise odds ratios (OR) of the different treatment comparisons for the outcome serious adverse events. Statistically significant results are in bold. Ischaemic preconditioning and pharmacological interventions were found to have significantly fewer serious adverse events compared to surgery alone

	Ischaemic preconditioning	**Pharmacological intervention**
Surgery alone	**OR 0.65; 95% CI 0.44 to 0.98**	**OR 0.49; 95% CI 0.35 to 0.69**
Ischaemic preconditioning	-	OR 0.75; 95% CI 0.44 to 1.27

Table A.18: Sensitivity analysis – larger groups. Pairwise mean differences (MD) of the different treatment comparisons for the outcome operative blood loss. Statistically significant results are in bold. Ischaemic preconditioning had significantly lower operative blood loss compared to surgery alone, hypothermia, and pharmacological interventions. In addition, hypothermia and pharmacological interventions had significantly higher operative blood loss compared to surgery alone.

	Hypothermia	**Ischaemic preconditioning**	**Pharmacological intervention**
Surgery alone	**MD 247.4 95% CI 143.7 to 351.1**	**MD -35.9 95% CI -53.32 to -18.48**	**MD 139.2 95% CI 107.23 to 171.17**
Hypothermia	-	**MD -283.3 95% CI -388.46 to -178.14**	MD -108.2 95% CI -216.72 to 0.32
Ischaemic preconditioning	-	-	**MD 175.1 95% CI 138.7 to 211.5**

Figure A.30: Sensitivity analysis – larger groups. Probability of being best treatment for the outcome operative blood loss. Ischaemic preconditioning was confirmed best treatment for operative blood loss with 100% probability.

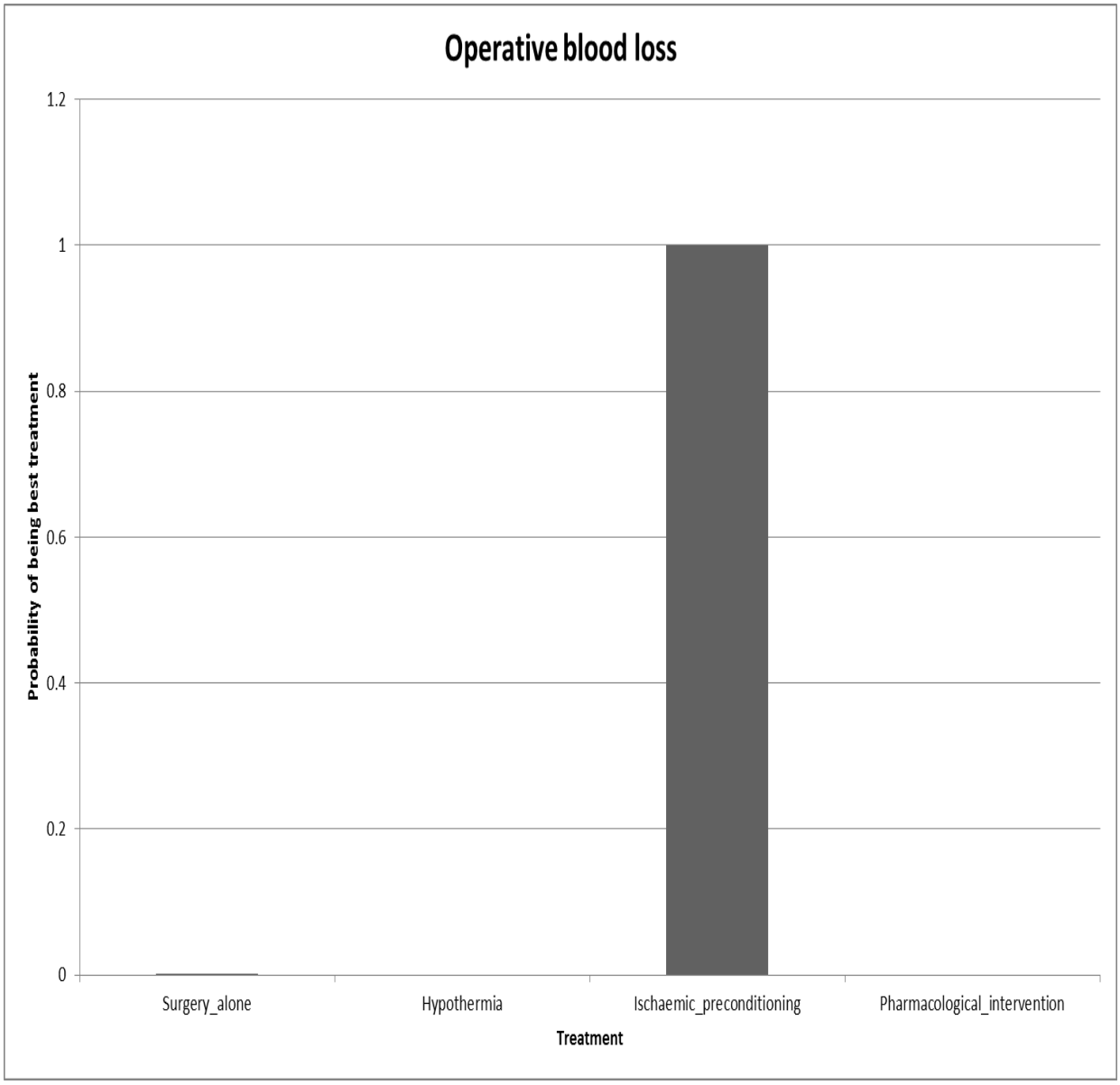
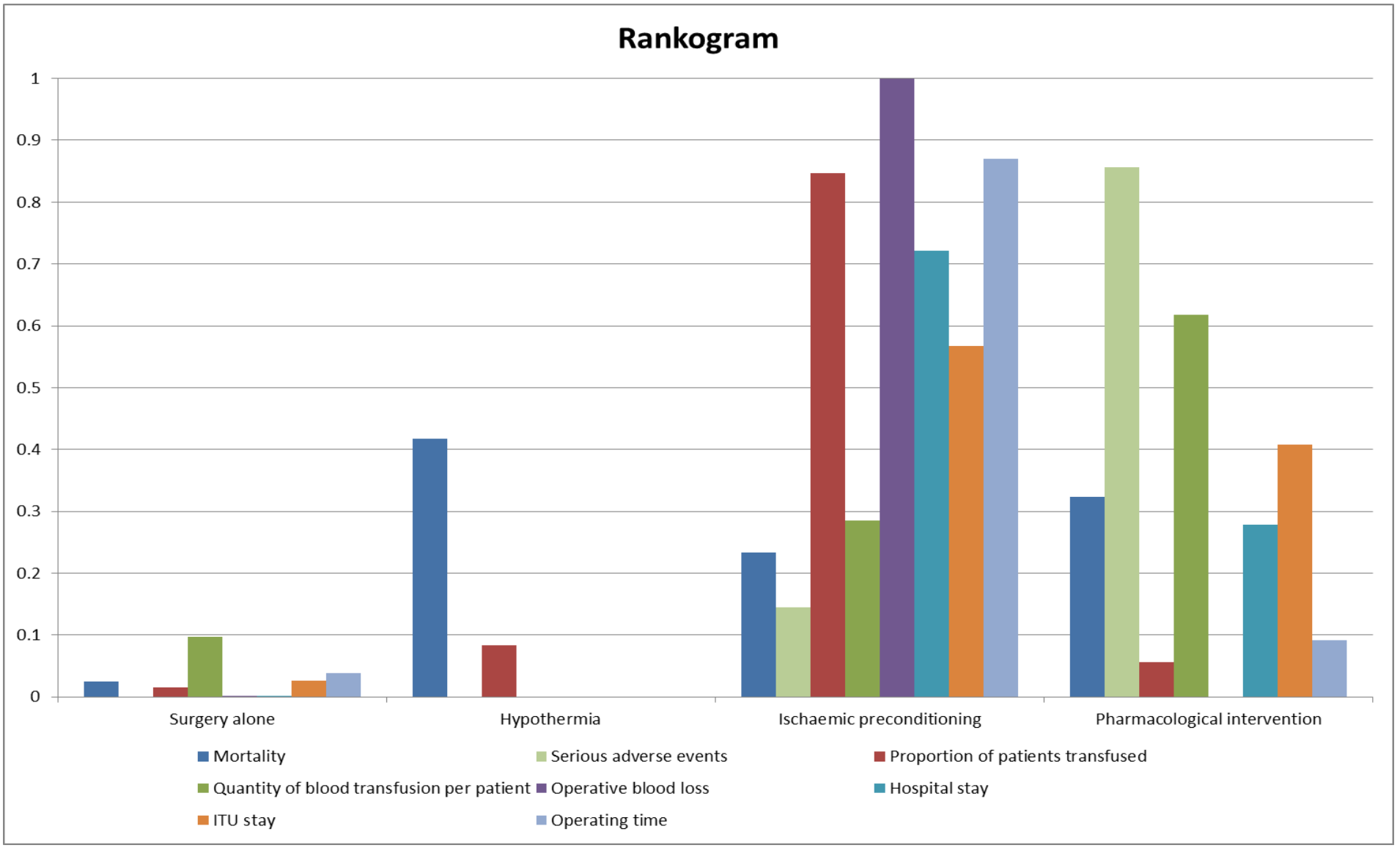


Figure A.31: Sensitivity analysis – larger groups. Rankogram showing the probability that a treatment group is best for each outcome.



A.3.5. Sensitivity network meta-analysis – only pharmacological interventions

A network meta-analysis was performed comparing the classes of pharmacological interventions, and another analysis comparing the individual pharmacological interventions, thus excluding ischaemic preconditioning and hypothermia from the analysis.

Comparing the classes of pharmacological interventions aiming to decrease IR injury during liver resection showed no significant difference between the classes of pharmacological interventions in mortality, number of patients transfused, and ITU stay. Cardiovascular modulators were found to have significantly fewer serious adverse events compared to surgery alone. Also, the miscellaneous group was found to have significantly fewer serious adverse events compared to the surgery alone and increased hepatic glycogen groups. The pairwise comparisons for serious adverse events are shown in Table A.19. Furthermore, the antioxidants group and cardiovascular modulators group had a significantly shorter length of hospital stay compared to the surgery alone and steroid groups. The increased hepatic glycogen group had significantly shorter operating time compared to the steroids and miscellaneous groups. Regarding operative blood loss, the surgery alone group had significantly lower operative blood loss compared to the antioxidants, immunomodulators, cardiovascular modulators, steroids, increased hepatic glycogen, and miscellaneous groups. The surgery alone group had a high probability (99%) of being the best treatment for operative blood loss. The immunomodulators and miscellaneous groups had significantly higher operative blood loss compared to the steroids and increased hepatic glycogen groups. The pairwise comparisons for operative blood loss are shown in Table A.20, and the probability of being best treatment is shown in Figure A.32. Finally, steroids were found to need a significantly lower quantity of blood transfusion compared to the surgery alone, antioxidants, increased hepatic glycogen, and miscellaneous groups.

Sensitivity network meta-analysis comparing the individual pharmacological interventions aiming to decrease IR injury found no significant difference between the individual interventions in mortality, number of patients transfused, and ITU stay.

Sevoflurane, verapamil, and gabexate mesilate had significantly fewer serious adverse events compared to surgery alone and pentoxifylline. Regarding hospital stay, surgery alone and steroids had a significantly longer hospital stay compared to trimetazidine and melatonin. Furthermore, vitamin E was found to have a significantly shorter operating time compared to amrinone and branched chain aminoacids. As in the previous analysis, the surgery alone group had significantly lower operative blood loss compared to steroids, verapamil, S-adenosyl-L-methionine, insulin, branched chain aminoacids, gabexate mesilate, and melatonin. Finally, vitamin E and steroids, resulted in significantly lower quantity of blood transfusion compared to surgery alone, sevoflurane, mannitol, insulin, and melatonin.

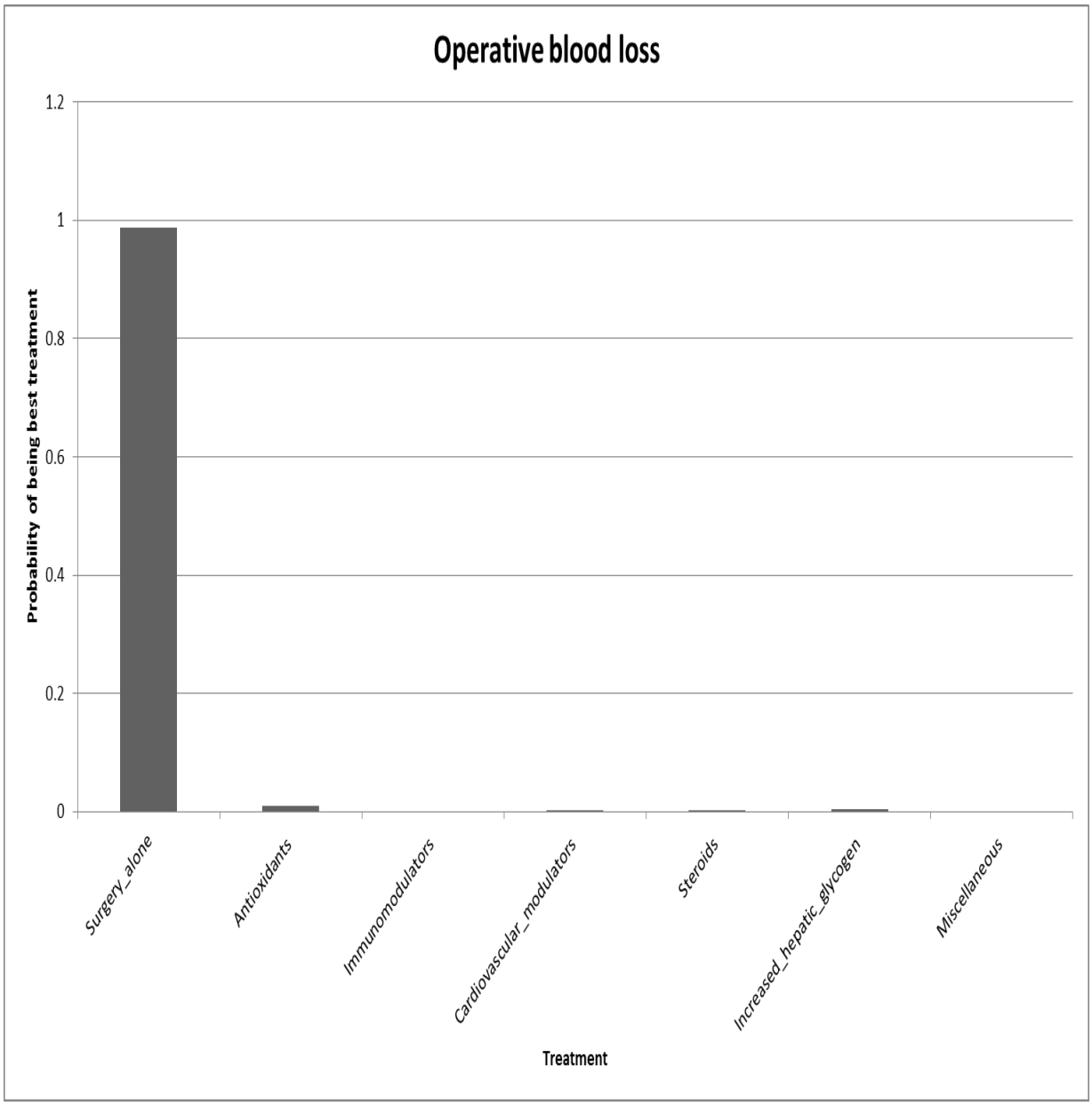
Table A.19: Sensitivity analysis – classes of pharmacological interventions. Pairwise odds ratios (OR) of the different treatment comparisons for the outcome serious adverse events (95% confidence intervals). Statistically significant results are in bold. Cardiovascular modulators were found to have significantly fewer serious adverse events compared to surgery alone. Also, the miscellaneous group was found to have significantly fewer serious adverse events compared to the surgery alone and increased hepatic glycogen groups.

	Antioxidants	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	OR 0.53 (0.19 to 1.47)	OR 0.67 (0.33 to 1.34)	**OR 0.4 (0.18 to 0.88)**	OR 0.66 (0.32 to 1.34)	OR 0.68 (0.15 to 3.09)	**OR 0.21 (0.08 to 0.51)**
Antioxidants	-	OR 1.26 (0.37 to 4.31)	OR 0.74 (0.2 to 2.71)	OR 1.23 (0.36 to 4.27)	OR 1.28 (0.21 to 7.92)	OR 0.39 (0.1 to 1.51)
Immunomodulators	-	-	OR 0.59 (0.2 to 1.71)	OR 0.98 (0.36 to 2.66)	OR 1.02 (0.19 to 5.38)	**OR 0.31 (0.1 to 0.96)**
Cardiovascular modulators	-	-	-	OR 1.66 (0.57 to 4.85)	OR 1.73 (0.31 to 9.54)	OR 0.52 (0.15 to 1.74)
Steroids	-	-	-	-	OR 1.04 (0.2 to 5.54)	OR 0.31 (0.1 to 1)
Increased hepatic glycogen	-	-	-	-	-	OR 0.3 (0.05 to 1.75)

Table A.20: Sensitivity analysis – classes of pharmacological interventions. Pairwise mean differences (MD) of the different treatment comparisons for the outcome operative blood loss (95% confidence intervals). Statistically significant results are in bold. Regarding operative blood loss, the surgery alone group had significantly lower operative blood loss compared to the antioxidants, immunomodulators, cardiovascular modulators, steroids, increased hepatic glycogen, and miscellaneous groups. The immunomodulators and miscellaneous groups had significantly higher operative blood loss compared to the steroids and increased hepatic glycogen groups.

	Antioxidants	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	**MD 207.8 (34.85 to 380.75)**	**MD 216.1 (125.8 to 306.4)**	**MD 137.1 (56.82 to 217.38)**	**MD 79.15 (32.42 to 125.88)**	**MD 92.08 (25.36 to 158.8)**	**MD 210.4 (118.59 to 302.21)**
Antioxidants	-	MD 8.3 (-186.8 to 203.4)	MD -70.7 (-261.38 to 119.98)	MD -128.65 (-307.8 to 50.5)	MD -115.72 (-301.09 to 69.65)	MD 2.6 (-193.21 to 198.41)
Immunomodulators	-	-	MD -79 (-199.83 to 41.83)	**MD -136.95 (-238.62 to -35.28)**	**MD -124.02 (-236.29 to -11.75)**	MD -5.7 (-134.47 to 123.07)
Cardiovascular modulators	-	-	-	MD -57.95 (-150.84 to 34.94)	MD -45.02 (-149.41 to 59.37)	MD 73.3 (-48.66 to 195.26)
Steroids	-	-	-	-	MD 12.93 (-68.52 to 94.38)	**MD 131.25 (28.24 to 234.26)**
Increased hepatic glycogen	-	-	-	-	-	**MD 118.32 (4.83 to 231.81)**

Figure A.32: Sensitivity analysis – classes of pharmacological interventions. Probability of being best treatment for the outcome operative blood loss. The surgery alone group had a high probability (99%) of being the best treatment for operative blood loss.



A.3.6. Metaregression – percentage of cirrhotic livers

A metaregression was performed based on the percentage of cirrhotic livers included in each trial. No significant difference was identified between the classes of interventions aiming to decrease IR during liver resection with regards to mortality, proportion of patients transfused, quantity of blood transfused per patient, operating time, hospital stay, and ITU stay. The surgery alone group was found to have significantly more serious adverse events compared to the ischaemic preconditioning, antioxidants, and miscellaneous groups. Also, the miscellaneous group had significantly fewer serious adverse events compared to the ischaemic preconditioning, immunomodulators, and cardiovascular modulators group. Moreover, the immunomodulators and miscellaneous groups of interventions were found to have significantly higher operative blood loss compared to the surgery alone, ischaemic preconditioning, steroids, and increased hepatic glycogen groups. The miscellaneous group also had significantly higher operative blood loss compared to the antioxidants and cardiovascular modulators groups. In addition, ischaemic preconditioning had significantly lower operative blood loss compared to the surgery alone group. The pairwise comparisons for the outcomes serious adverse events and operative blood loss are shown in Table A.21 and Table A.22 respectively.

Table A.21: Metaregression – percentage of cirrhotic livers. Pairwise odds ratios (OR) of the different treatment comparisons for the outcome serious adverse events (95% confidence intervals). Statistically significant results are in bold. The surgery alone group was found to have significantly more serious adverse events compared to the ischaemic preconditioning, antioxidants, and miscellaneous groups. Also, the miscellaneous group had significantly fewer serious adverse events compared to the ischaemic preconditioning, immunomodulators, and cardiovascular modulators group.

	Ischaemic preconditioning	**Antioxidants**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Miscellaneous**
Surgery alone	**OR 0.55 (0.36 to 0.85)**	**OR 0.35 (0.12 to 0.99)**	OR 0.63 (0.31 to 1.29)	OR 1.19 (0.36 to 3.87)	OR 0.26 (0.06 to 1.12)	**OR 0.16 (0.06 to 0.41)**
Ischaemic preconditioning	-	OR 0.62 (0.2 to 1.94)	OR 1.14 (0.5 to 2.61)	OR 2.15 (0.61 to 7.54)	OR 0.47 (0.1 to 2.16)	**OR 0.29 (0.1 to 0.81)**
Antioxidants	-	-	OR 1.82 (0.51 to 6.5)	OR 3.44 (0.71 to 16.73)	OR 0.75 (0.12 to 4.56)	OR 0.46 (0.11 to 1.9)
Immunomodulators	-	-	-	OR 1.89 (0.47 to 7.5)	OR 0.41 (0.08 to 2.1)	**OR 0.25 (0.08 to 0.83)**
Cardiovascular modulators	-	-	-	-	OR 0.22 (0.03 to 1.43)	**OR 0.13 (0.03 to 0.61)**
Steroids	-	-	-	-	-	OR 0.62 (0.11 to 3.56)

Table A.22: Metaregression – percentage of cirrhotic livers. Pairwise mean differences (MD) of the different treatment comparisons for the outcome operative blood loss (95% confidence intervals). Statistically significant results are in bold. The immunomodulators and miscellaneous groups of interventions were found to have significantly higher operative blood loss compared to the surgery alone, ischaemic preconditioning, steroids, and increased hepatic glycogen groups. The miscellaneous group also had significantly higher operative blood loss compared to the antioxidants and cardiovascular modulators groups. In addition, ischaemic preconditioning had significantly lower operative blood loss compared to the surgery alone group.

	Ischaemic preconditioning	**Antioxidants**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	**MD -33.21 (-52.33 to -14.09)**	MD -7.07 (-189.54 to 175.41)	**MD 173.4 (76.2 to 270.6)**	MD -2.94 (-152.29 to 146.41)	MD 1.57 (-84.95 to 88.08)	MD -81.53 (-201.62 to 38.56)	**MD 206.9 (113.07 to 300.73)**
Ischaemic preconditioning	-	MD 26.15 (-157.33 to 209.62)	**MD 206.61 (107.55 to 305.67)**	MD 30.27 (-120.3 to 180.84)	MD 34.78 (-53.83 to 123.38)	MD -48.32 (-169.92 to 73.28)	**MD 240.11 (144.36 to 335.86)**
Antioxidants	-	-	MD 180.47 (-26.28 to 387.21)	MD 4.12 (-231.68 to 239.93)	MD 8.63 (-193.32 to 210.58)	MD -74.47 (-292.91 to 143.98)	**MD 213.97 (8.78 to 419.15)**
Immunomodulators	-	-	-	MD -176.34 (-354.54 to 1.85)	**MD -171.84 (-301.96 to -41.71)**	**MD -254.93 (-409.42 to -100.44)**	MD 33.5 (-101.59 to 168.59)
Cardiovascular modulators	-	-	-	-	MD 4.51 (-168.09 to 177.11)	MD -78.59 (-270.23 to 113.06)	**MD 209.84 (33.46 to 386.22)**
Steroids	-	-	-	-	-	MD -83.1 (-231.1 to 64.91)	**MD 205.34 (77.71 to 332.96)**
Increased hepatic glycogen	-	-	-	-	-	-	**MD 288.43 (136.03 to 440.83)**

A.3.7. Metaregression – percentage of major liver resections

A metaregression was performed based on the percentage of major liver resections performed in each trial. No significant difference was identified between the classes of interventions aiming to decrease IR injury during hepatectomy with regards to mortality, operating time, and ITU stay. Regarding serious adverse events, ischaemic preconditioning, cardiovascular modulators and miscellaneous classes of interventions were found to have significantly fewer serious adverse events compared to surgery alone. Steroids had significantly more serious adverse events compared to the miscellaneous class. Furthermore, ischaemic preconditioning was found to have significantly shorter length of hospital stay compared to surgery alone. Also, the ischaemic preconditioning group was found to have significantly fewer patients needing blood transfusion compared to the surgery alone group. Moreover, ischaemic preconditioning was found to have significantly lower operative blood loss compared to the surgery alone, immunomodulators, cardiovascular modulators, steroids, and increased hepatic glycogen groups. Surgery alone had significantly lower operative blood loss compared to immunomodulators, cardiovascular modulators, and increased hepatic glycogen groups. In addition, the increased hepatic glycogen group had significantly higher operative blood loss compared to the hypothermia, antioxidants, steroids, and miscellaneous groups. The immunomodulators group resulted in significantly lower quantity of blood transfusion compared to the surgery alone, ischaemic preconditioning, and antioxidants groups. The pairwise comparisons for the outcomes serious adverse events and operative blood loss are shown in Table A.23 and Table A.24 respectively.

Table A.23: Metaregression – percentage of major liver resections. Pairwise odds ratios (OR) of the different treatment comparisons for the outcome serious adverse events (95% confidence intervals). Statistically significant results are in bold. Ischaemic preconditioning, cardiovascular modulators and miscellaneous classes of interventions were found to have significantly fewer serious adverse events compared to surgery alone. Steroids had significantly more serious adverse events compared to the miscellaneous class.

	Ischaemic preconditioning	**Antioxidants**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	**OR 0.6 (0.39 to 0.91)**	OR 0.51 (0.16 to 1.62)	OR 0.56 (0.26 to 1.18)	**OR 0.34 (0.13 to 0.87)**	OR 0.79 (0.36 to 1.7)	OR 0.82 (0.18 to 3.78)	**OR 0.2 (0.07 to 0.55)**
Ischaemic preconditioning	-	OR 0.86 (0.25 to 2.93)	OR 0.93 (0.39 to 2.2)	OR 0.57 (0.2 to 1.59)	OR 1.32 (0.55 to 3.17)	OR 1.37 (0.28 to 6.7)	OR 0.33 (0.11 to 1)
Antioxidants	-	-	OR 1.08 (0.27 to 4.27)	OR 0.66 (0.15 to 2.91)	OR 1.53 (0.38 to 6.1)	OR 1.59 (0.24 to 10.79)	OR 0.38 (0.08 to 1.79)
Immunomodulators	-	-	-	OR 0.61 (0.18 to 2.03)	OR 1.41 (0.48 to 4.14)	OR 1.47 (0.27 to 8.09)	OR 0.35 (0.1 to 1.26)
Cardiovascular modulators	-	-	-	-	OR 2.33 (0.69 to 7.87)	OR 2.43 (0.4 to 14.62)	OR 0.58 (0.14 to 2.35)
Steroids	-	-	-	-	-	OR 1.04 (0.19 to 5.78)	**OR 0.25 (0.07 to 0.91)**
Increased hepatic glycogen	-	-	-	-	-	-	OR 0.24 (0.04 to 1.51)

Table A.24: Metaregression – percentage of major liver resections. Pairwise mean differences (MD) of the different treatment comparisons for the outcome operative blood loss (95% confidence intervals). Statistically significant results are in bold. Ischaemic preconditioning was found to have significantly lower operative blood loss compared to the surgery alone, immunomodulators, cardiovascular modulators, steroids, and increased hepatic glycogen groups. Surgery alone had significantly lower operative blood loss compared to immunomodulators, cardiovascular modulators, and increased hepatic glycogen groups. In addition, the increased hepatic glycogen group had significantly higher operative blood loss compared to the hypothermia, antioxidants, steroids, and miscellaneous groups.

	Hypothermia	**Ischaemic preconditioning**	**Antioxidants**	**Immunomodulators**	**Cardiovascular modulators**	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	MD 12.09 (-167.5 to 191.68)	**MD -36.18 (-58.07 to -14.29)**	MD 26.47 (-183.25 to 236.19)	**MD 208.9 (120.8 to 297)**	**MD 136.1 (54.09 to 218.11)**	MD 51.23 (-0.02 to 102.48)	**MD 278.4 (147.65 to 409.15)**	MD 13.66 (-147.57 to 174.89)
Hypothermia	-	MD -48.27 (-229.19 to 132.65)	MD 14.38 (-261.73 to 290.49)	MD 196.81 (-3.23 to 396.85)	MD 124.01 (-73.42 to 321.44)	MD 39.14 (-147.63 to 225.91)	**MD 266.31 (44.16 to 488.46)**	MD 1.57 (-239.78 to 242.92)
Ischaemic preconditioning	-	-	MD 62.65 (-148.21 to 273.51)	**MD 245.08 (154.3 to 335.86)**	**MD 172.28 (87.4 to 257.16)**	**MD 87.41 (31.68 to 143.14)**	**MD 314.58 (182.01 to 447.15)**	MD 49.84 (-112.87 to 212.55)
Antioxidants	-	-	-	MD 182.43 (-45.04 to 409.9)	MD 109.63 (-115.55 to 334.81)	MD 24.76 (-191.13 to 240.65)	**MD 251.93 (4.79 to 499.07)**	MD -12.81 (-277.34 to 251.72)
Immunomodulators	-	-	-	-	MD -72.8 (-193.16 to 47.56)	**MD -157.67 (-259.6 to -55.74)**	MD 69.5 (-88.16 to 227.16)	**MD -195.24 (-378.97 to -11.51)**
Cardiovascular modulators	-	-	-	-	-	MD -84.87 (-181.58 to 11.84)	MD 142.3 (-12.04 to 296.64)	MD -122.44 (-303.33 to 58.45)
Steroids	-	-	-	-	-	-	**MD 227.17 (86.73 to 367.61)**	MD -37.57 (-206.75 to 131.61)
Increased hepatic glycogen	-	-	-	-	-	-	-	**MD -264.74 (-472.32 to -57.16)**

A.4 DISCUSSION

This network meta-analysis analysed data from 44 RCTs, comparing eight classes of interventions aimed at decreasing IR injury during liver resection and a control group which was surgery alone. There was no statistically significant difference in mortality between the groups, and that was persistent during sensitivity analysis. The overall mortality found in this review was 1.3%, which is lower compared to the 3% to 4% overall mortality reported by large case series of liver resections.[45, 46, 63] There is no clear reason why the mortality is lower in the trials included in this review, although, there is the possibility that the overall outcomes were better because patients were included in a trial, even if they were in the control group. Studies assessing whether there were harmful or beneficial effects to patients from participating in research trials gave contradictory results with some studies suggesting the outcomes of patients participating and not participating in trials were similar,[393-395] and other studies suggesting that clinical trials have a positive effect on the outcome of participants.[396-398] There was no evidence to suggest that patients of lower anaesthetic risk were selectively recruited in the included RCTs. Nevertheless, the included trials were not powered to measure differences in mortality. If a trial was designed to compare short-term mortality after liver resection between an intervention aiming to decrease IR injury and control, a sample size of approximately 26,851 patients per group would be needed to detect a 20% reduction in mortality, i.e. a reduction in mortality from 1.3% in the control group to 1.04% in the intervention group, based on alpha-error of 0.05 and 80% power.

The rate of serious adverse events reported in this review was 17.2% which is slightly lower compared to other series of liver resection.[45, 399, 400] The interventions aiming to decrease IR injury during hepatectomy are not treatments for serious adverse events, but through their mechanism of action and by decreasing the injury to the liver during surgery, may prevent or reduce the postoperative complication rate. Three groups of interventions – ischaemic preconditioning, cardiovascular modulators, and miscellaneous group – were found to have fewer serious adverse events compared to the surgery alone group. Sensitivity analysis confirmed ischaemic preconditioning to have fewer serious adverse events compared to surgery alone. The miscellaneous group had fewer serious adverse events compared to ischaemic preconditioning, immunomodulators, and steroids. Although there was a high probability that the

miscellaneous group of interventions was best in reducing or preventing serious adverse events (74% chance), sensitivity analysis performed showed none of the individual interventions within the miscellaneous group to have a high probability of being the best intervention in preventing serious adverse events. Overall, no individual intervention had a probability higher than 40% of being best intervention in reducing serious adverse events. Evaluation with sensitivity analyses showed sevoflurane (from the miscellaneous group of interventions) to result in fewer serious adverse events compared to surgery alone, ischaemic preconditioning, and pentoxifylline, possibly explaining the findings of the overall network meta-analysis regarding the miscellaneous group. Also, verapamil (from the cardiovascular modulators group) and gabexate mesilate (from the immunomodulators group) were found both to result in significantly less serious adverse events compared to surgery alone and pentoxifylline.

All interventions in this review aimed at reducing IR injury during hepatectomy. But, if this were their sole mechanism of action we would expect all end points with a single intervention to be beneficial or not. Since this is not the case, it may suggest multiple additional actions for each intervention with multiple secondary effects. Hence, for each intervention there is the possibility of improvement in one complication (e.g. blood loss), without improvement in other outcomes (e.g. hospital stay or serious adverse events). For example, the antioxidant group of interventions (e.g. antioxidant multivitamin, allopurinol, mannitol, melatonin, propofol, vitamin E) is thought to decrease IR injury by reducing the amount of oxygen free radicals or reactive oxygen species produced during the ischaemic-reperfusion phase. Nevertheless, the beneficial effects of allopurinol is also thought to be mediated by improving resynthesis of ATP during reperfusion after ischaemia, and by preserving hepatocyte function.[390, 401] Mannitol is an osmotic diuretic with free radical–scavenging properties, which has been shown to reduce the extent of ischaemic injury and improve myocardial, renal, and cerebral function.[377] Propofol, a widely used anaesthetic agent, has been shown to reduce free radical production under ischaemia–reperfusion conditions,[87, 402] but may also have a protective effect against hepatic injury and improve liver metabolic function recovery.[87]

Ischaemic preconditioning is the mechanism by which brief periods of ischaemia (hepatic vascular occlusion) followed by reperfusion of the organ results in the ability of

the organ to withstand a subsequent prolonged period of ischaemia.[92] There have been trials in the literature demonstrating the beneficial effects of ischaemic preconditioning on the outcomes of liver resection surgery in patients with background healthy livers as well as those with background cirrhotic or steatotic livers by showing a decrease in postoperative liver enzymes which are markers for liver parenchymal injury.[67, 68, 379, 380, 403] Nevertheless, trials have not shown a significant benefit in clinical end points due to ischaemic preconditioning, reporting no statistically significant difference in mortality, morbidity, liver failure, hospital stay, or ITU stay.[67, 68, 80, 368, 371] Although the exact mechanism of hepatic protection by ischaemic preconditioning is not known, it is considered to be multifactorial, including preservation of post-reperfusion adenosine triphosphate (ATP) content in liver tissue, inhibition of apoptosis, decrease in caspase-3 (one of the mediators of apoptosis), activation of polymorphonuclear leukocytes, and release of substances such as metabolites of ATP degradation (e.g. adenosine) or nitric oxide (NO) by the ischaemic tissue which protect the liver against the subsequent prolonged ischaemic insult.[68, 379, 391, 404] Furthermore, ischaemic preconditioning is found to result in improved cardiovascular stability by lowering the need for catecholamines after liver reperfusion without affecting the blood sparing benefits of the Pringle manoeuver.[67]

The interventions belonging in the immunomodulators may decrease IR injury during hepatectomy through a range of actions: inhibition of neutrophil activation (gabexate mesilate, sivelestat), suppression of acute inflammatory cytokine reaction (gabexate mesilate, Prostaglandin E1, pentoxifylline, sivelestat), antioxidant action (gabexate mesilate), and anticoagulatory properties (gabexate mesilate, Prostaglandin E1, pentoxifylline).[374-376, 384, 389, 405] Furthermore, the cardiovascular modulators group of interventions may reduce IR injury through a positive inotropic effect (amrinone), or through vasodilation enhancing splanchnic blood flow (amrinone, dopamine, dopexamine), or by preventing vasoconstriction and platelet aggregation (OKY 046).[90, 383, 385, 386] Verapamil is a calcium channel blocker which can maintain intracellular calcium homeostasis, prevent activation of Kupffer cells and release of cytokines, and attenuate IR injury of several organs including the liver.[91, 406-409] The miscellaneous group contained drugs with multiple mechanisms of action. For example, sevoflurane, whose benefits were first shown in cardiac surgery, is thought to decrease IR injury through stimulation of adenosine receptors and subsequent activation of protein kinase

C and increased production of nitric oxide and free oxygen radicals.[86, 370, 406, 410-412] Although sevoflurane, verapamil, and gabexate mesilate were found to have fewer serious adverse events during sensitivity analysis, none of these treatments significantly reduced ITU or hospital stay, which would be anticipated if an intervention made a significant reduction in serious adverse events.

On the other hand, ischaemic preconditioning showed multiple benefits including shorter hospital stay compared to the surgery alone group (i.e. versus no ischaemic preconditioning), decreased blood loss compared to all other interventions, shorter operative time (compared to steroids), and the highest probability of being best treatment for reducing the operative time (87%). The decreased operative time is perhaps counter-intuitive as the ischaemic preconditioning is in effect an additional operative manoeuver that takes additional time. However, ischaemic preconditioning used in combination with intermittent or continuous vascular occlusion, may decrease operative time by decreasing the time taken for parenchymal transection because of reduced blood loss during the surgery. The time necessary for haemostasis may be shortened and subsequent operative manoeuvers (such as parenchymal dissection) facilitated.[371, 413] The reduced operative time related to ischaemic preconditioning may reduce the costs of surgery and possibly allow more surgeries to be performed.

The main cause of IR injury during elective liver resection is blood inflow occlusion to the liver (e.g. with the Pringle manoeuver) which is used to decrease the blood loss and blood transfusion requirements. Intraoperative haemorrhage remains one of the major risks during liver resections, and increased operative blood loss and perioperative blood transfusion are directly related to higher morbidity and mortality.[45, 46, 64, 65] Therefore, it would be important for any treatment aiming to decrease IR injury to also reduce operative blood loss. A decrease in blood loss with an associated decrease in blood transfusion, adverse events, and hospital stay, may also result in decreased costs. This study showed that ischaemic preconditioning had significantly lower operative blood loss compared to the surgery alone group and compared to all other interventions, and it had a high probability of being the best treatment for this outcome. These findings persisted during sensitivity analysis. Another important finding during analysis of this outcome was that the surgery alone group (control group) had significantly lower operative blood loss compared to all other interventions, except the ischaemic

preconditioning group. Therefore, not only was ischaemic preconditioning the only intervention to significantly reduce blood loss, but also all other interventions resulted in significantly higher operative blood loss compared to the surgery alone group. These results were persistent during sensitivity analyses and would suggest that other than ischaemic preconditioning the other interventions are ineffectual at reducing blood loss.

The results on operative blood loss were not reciprocated on blood transfusion requirements (proportion of patients transfused and quantity of blood transfusion), where there were no significant differences between interventions, apart from a significantly lower proportion of patients transfused with ischaemic preconditioning compared to steroids. The fewer people transfused with ischaemic preconditioning compared to steroids is most likely due to reduced bleeding caused by ischaemic preconditioning as suggested in the above paragraph, rather than increased blood loss caused by steroids. RCTs comparing steroids versus controls showed no significant difference in operative blood loss and blood transfusion requirements.[84, 85, 366, 367] On the other hand, some RCTs comparing ischaemic preconditioning versus controls showed no statistically significant difference in operative blood loss and blood transfusion requirements,[68, 80, 258, 379, 391] and other RCTs demonstrated significantly reduced bleeding and/or significantly decreased blood transfusion requirements with ischaemic preconditioning compared to controls.[76, 371, 387] The variance in the results of RCTs regarding operative blood loss for ischaemic preconditioning may be due to trial size (i.e. not enough patients included in the trial to show statistical significance), different patient selection criteria, different methods of measuring blood loss, and variability of ischaemic preconditioning protocols between trials (e.g. variability in the timing of ischaemic preconditioning and the type of vascular occlusion performed during liver resection).

This is the first network meta-analysis of IR injury therapies in liver resection surgery, but previously there have been standard pairwise meta-analyses comparing individual components aiming to decrease IR injury. The advantage of network meta-analysis over standard pairwise meta-analysis is that it facilitates indirect comparisons of multiple interventions that have not been studied in a head-to-head fashion.[148] A network meta-analysis may also yield more reliable and definitive results than would a pairwise meta-analysis.[148] One pairwise meta-analysis included five RCTs which compared one

pharmacological agent versus another pharmacological agent (a total of 9 different pharmacological agents).[71] The meta-analysis suggested that there was no significant difference between the groups in mortality, liver failure, or perioperative morbidity.[71] Nevertheless, a statistical meta-analysis of the data with forest plots could not be performed since indirect comparisons of the different pharmacological agents were not possible with a pairwise meta-analysis.[71] This deficiency has been addressed by the current network meta-analysis.

Another pairwise meta-analysis included fifteen RCTs comparing any pharmacological agent versus placebo or no pharmacological agent.[364] The pharmacological agents included in the pairwise meta-analysis were: methylprednisolone, multivitamin, antioxidant infusion, vitamin E infusion, amrinone, prostaglandin E1, pentoxifylline, mannitol, trimetazidine, dextrose, allopurinol, and OKY 046.[364] Again, similar to the previous pairwise meta-analysis, indirect comparisons between groups could not be performed, and the only statistical meta-analysis performed was of four RCTs comparing Prostaglandin E1 versus placebo, and a separate meta-analysis of three studies comparing Methylprednisolone versus control.[364] The meta-analysis showed no significant differences between the groups in mortality, liver failure, or perioperative morbidity. The authors reported that trimetazidine had a significantly shorter hospital stay than control, and that trimetazidine, methylprednisolone, and dextrose reduced the enzyme markers of liver injury compared with controls.[364] Again the deficiencies of the pairwise meta-analysis have been addressed by the current network meta-analysis which has shown no significant clinical benefit for any of the pharmacological interventions included in the pairwise meta-analysis.

A meta-analysis comparing ischaemic preconditioning versus no ischaemic preconditioning found no significant difference in mortality, morbidity, hospital stay, or ITU stay but showed reduced blood transfusion requirements with ischaemic preconditioning.[368] Another meta-analysis comparing trials of ischaemic preconditioning versus intermittent vascular inflow occlusion showed, similar to this network meta-analysis, shorter operative time with ischaemic preconditioning, and no difference in mortality, morbidity, and hospital stay.[414] Both previous meta-analyses[368, 414] did not show a significant decrease in blood loss with ischaemic preconditioning, possibly due to a lower number of RCTs included (4 RCTs[368] and 5 RCTs[414]).

Furthermore, a meta-analysis evaluating ischaemic preconditioning found, similar to this meta-analysis, no significant difference in mortality, morbidity, liver failure, or length of ITU stay between *ischaemic preconditioning plus continuous clamping* versus *continuous clamping*, or between *ischaemic preconditioning plus (continuous clamping or intermittent clamping)* versus *intermittent clamping*.[413] The same meta-analysis reported significantly shorter length of hospital stay and a significant reduction in the proportion of patients having blood transfusion with *ischaemic preconditioning plus continuous clamping* versus *continuous clamping*.[413] Finally, similar to this network meta-analysis, shorter operative time was reported with *ischaemic preconditioning plus (continuous clamping or intermittent clamping)* versus *intermittent clamping*.[413] Overall, the results of this network meta-analysis agree with the results of previous meta-analyses and RCTs, and would suggest multiple beneficial clinical end points to ischaemic preconditioning treatment, indicating that ischaemic preconditioning should be introduced into routine clinical practise during liver resection surgery. Any small variations in the results may have resulted due to variation between trials possibly reflecting trial size (e.g. not enough patients included in a trial to show statistical significance), patient selection criteria and case mix, different methods of measurement (e.g. methods of measuring blood loss), protocols (e.g. variability in the timing of ischaemic preconditioning and the type of vascular occlusion performed during liver resection), and end points evaluated.

In all the trials included in the current review, where ischaemic preconditioning was used to decrease IR injury, ischaemic preconditioning was performed with liver vascular inflow occlusion (also called Pringle manoeuver or portal triad clamping). Nevertheless, there was variability between trials in the timing of ischaemic preconditioning and the type of vascular occlusion performed during liver resection. The downside of this is that it does not allow for the optimal ischaemic preconditioning protocol to be determined accurately or even whether some protocols were ineffective. In some trials, ischaemic preconditioning was performed with 10 minutes of vascular inflow occlusion and 10 minutes of reperfusion,[67, 68, 76, 79, 80, 258, 317, 371, 382, 387] whereas in other trials ischaemic preconditioning was performed with 5 minutes of vascular inflow occlusion and 5 minutes of reperfusion.[372, 379, 380] Furthermore, in some trials ischaemic preconditioning was followed by vascular inflow occlusion (or Pringle manoeuver) for liver resection,[67, 68, 76, 258, 317, 371, 372, 379, 380, 382] whereas in other trials it was followed by selective hepatic

vascular exclusion (occlusion of inflow to the hemi-liver and outflow from the hemi-liver that is being resected)[80, 387] or hepatic vascular exclusion (i.e. simultaneous clamping of the portal triad and the main hepatic veins).[79]

Sensitivity network meta-analysis comparing only pharmacological interventions (i.e. excluding ischaemic preconditioning and hypothermia), showed no significant differences between the individual pharmacological interventions in mortality, number of patients transfused, and ITU stay. Similar to the overall analysis, cardiovascular modulators and the miscellaneous group were found to have fewer serious adverse events compared to surgery alone. Comparison of the individual pharmacological interventions, showed specifically sevoflurane, verapamil, and gabexate mesilate to have fewer serious adverse events compared to surgery alone and pentoxifylline, similar to the results of the overall analysis. It is not clear how these pharmacological interventions reduce serious adverse events and it is not sufficient to justify their use based on the findings of the current literature, and, therefore, more trials are required to further investigate the use of these pharmacological interventions during liver resection. Furthermore, similar to the findings of the overall analysis, the surgery alone group had lower operative blood loss compared to the antioxidants, immunomodulators, cardiovascular modulators, steroids, increased hepatic glycogen, and miscellaneous groups. Without ischaemic preconditioning in the analysis, the surgery alone group had a high probability (99%) of being the best treatment for operative blood loss in the analysis of only pharmacological interventions. This suggests that the pharmacological agents increase blood loss, and this apparent disadvantage should be weighed against any apparent benefit of pharmacological interventions, e.g. in reducing serious adverse events. A possible explanation in the increase in operative blood loss by these pharmacological agents is that by increasing the microvascular flow and perfusion of the liver in order to decrease IR injury, they result in increased overall blood flow and blood loss during hepatectomy.

Possible sources of bias in this network meta-analysis are the proportion of cirrhotic and steatotic livers included in each trial, and the proportion of patients undergoing major liver resections in each trial. Therefore, metaregressions were performed based on the proportion of cirrhotic livers and major liver resections included in each trial. Unfortunately, due to the low number of trials reporting on the number of steatotic

livers included (only 7 trials), a metaregression based on the proportion of steatotic livers was not possible. A metaregression based on the percentage of cirrhotic livers included in each trial showed no significant difference between the classes of interventions with regards to mortality, proportion of patients transfused, quantity of blood transfused per patient, operating time, hospital stay, and ITU stay. The metaregression based on the percentage of major liver resections performed in each trial showed no significant difference between the classes of interventions with regards to mortality, operating time, and ITU stay. Similar to the overall analysis, both metaregressions showed ischaemic preconditioning, cardiovascular modulators and miscellaneous classes of interventions to have fewer serious adverse events compared to surgery alone. In addition, ischaemic preconditioning was found to result in lower operative blood loss compared to the immunomodulators, miscellaneous, and surgery alone groups in the metaregression based on the number of cirrhotic livers, and compared to the immunomodulators, cardiovascular modulators, increased hepatic glycogen, and surgery alone groups in the metaregression based on the number of major liver resections. The latter metaregression also showed ischaemic preconditioning to result in fewer patients needing blood transfusion compared to surgery alone, and shorter length of hospital stay compared to surgery alone.

The results of the network meta-analysis did not allow one superior intervention to be identified. However, ischaemic preconditioning, which can be achieved without any requirement for equipment, costs, or additional expertise, has a high likelihood of being beneficial to the patients undergoing liver resection. Further RCTs are needed to confirm clinical benefit in order to allow ischaemic preconditioning to become standard practice during liver resection. Sensitivity analysis identified three drugs (sevoflurane, verapamil, and gabexate mesilate) which may reduce serious adverse events during elective liver resection. This network meta-analysis could be used to design future RCT's related to the treatment of IR injury during liver resection surgery and the impact of treatment on costs, quality of life, and long-term outcomes. RCTs comparing interventions aiming to decrease IR injury will require high number of patients to be recruited to identify statistically significant differences in outcomes (for example, approximately 2051 patients in each group would be needed to identify a 10% reduction in morbidity, i.e. reduction in morbidity from 43% in the control group to 38.7% in the intervention group, based on alpha-error of 0.05 and 80% power). To overcome this

problem, instead of a parallel design, a factorial trial design for an RCT may be used where multiple interventions ('factors') can be assessed in the same trial, reducing the overall sample size needed for the trial and allowing for exploration of interactions between multiple interventions.[415]

A.5 CONCLUSIONS

This network meta-analysis included 44 RCTs, and was performed to assess the comparative benefits and harms of different methods that aim to decrease IR injury during elective liver resection. There was no significant difference between the different interventions in mortality, quantity of blood transfusion, and ITU stay. Patients treated with ischaemic preconditioning, cardiovascular modulators, and miscellaneous interventions had significantly fewer serious adverse events compared to patients receiving surgery alone. Ischaemic preconditioning patients had significantly fewer transfusion proportions and shorter operative time than patients treated with steroids. Also, ischaemic preconditioning had significantly lower operative blood loss compared to all other interventions, and shorter length of hospital stay than surgery alone. Sensitivity analysis identified three drugs, sevoflurane (a volatile anaesthetic), verapamil (a calcium channel blocker), and gabexate mesilate (a thrombin inhibitor) which may reduce serious adverse events during elective liver resection, and further RCTs are needed to investigate these results. Importantly, ischaemic preconditioning showed promising results for most outcomes, and should be introduced into routine clinical practise during liver resection surgery.

LIST OF PUBLICATIONS AND PRESENTATIONS RESULTING FROM THIS THESIS

A meta-analysis comparing simultaneous versus delayed resections in patients with synchronous colorectal liver metastases.
Slesser AA, **Simillis C**, Goldin R, Brown G, Mudan S, Tekkis PP.
Published at **Surgical Oncology**, 2013 Mar; 22(1):36-47.
Oral presentation, British Association of Surgical Oncology, November 2012.
Poster presentation, European Society of Coloproctology, Belgrade, Serbia, September 2013.

Management of the hepatic lymph nodes during resection of liver metastases from colorectal cancer: a systematic review.
Koti R, **Simillis C**, Gurusamy K, Jacovides M, Davidson B.
Published at **Current Colorectal Cancer Reports**, 2013; 9:203-12.

Methods to decrease blood loss during liver resection: a network meta-analysis.
Simillis C, Li T, Vaughan J, Becker LA, Davidson BR, Gurusamy K.
Published at **The Cochrane Database of Systematic Reviews**, 2014 Apr ;4:CD010683.
Poster presentation at the 11th World Congress of the International Hepato-Pancreato-Biliary Association at Seoul, Korea, March 2014.

A Cochrane systematic review and network meta-analysis comparing treatment strategies aiming to decrease blood loss during liver resection.
Simillis C, Li T, Vaughan J, Becker LA, Davidson BR, Gurusamy K.
Published at **International Journal of Surgery**, 2015 Nov;23(Pt A):128-36.

A network meta-analysis comparing perioperative outcomes of interventions aiming to decrease ischemia reperfusion injury during elective liver resection.
Simillis C, Robertson FP, Afxentiou T, Davidson BR, Gurusamy K.
Published at **Surgery**, 2015. doi: 10.1016/j.surg.2015.10.011. [Epub ahead of print]
Oral presentation at the European-African Hepato-Pancreato-Biliary Association Congress at Manchester, UK, April 2015.

Is reporting the period of follow-up a source of bias in comparative trials?
Simillis C, Zertalis M, Davidson BR, Gurusamy K.
Written in preparation for submission to a journal.

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