***Corresponding author***
Dr Charles M Oliver
Royal College of Anaesthetists,
35 Red Lion Square,
London,
WC1R 4SG

**The association of pre-operative anaemia with morbidity and mortality after emergency laparotomy**

H. Boyd-Carson,[1] A. Shah,[2 3] A. Sugavanam,[4 5] J. Reid,[6] S. J. Stanworth[7 8] and C. M. Oliver[9 10]

*1 NELA Research Fellow, 9 NELA Academic Lead, Royal College of Anaesthetists, London, UK*
*2 NIHR Doctoral Research Fellow, 7 Professor, Radcliffe Department of Medicine, University of Oxford, Oxford, UK*
*3 Specialty Registrar, Nuffield Department of Anaesthesia, John Radcliffe Hospital, Oxford, UK*
*4 Consultant Anaesthetist, 6 Specialty Registrar, Department of Anaesthesia, Brighton and Sussex University Hospitals NHS Trust*
*5 Consultant Anaesthetist, Danube Hospital, Vienna, Austria*
*8 Consultant Haematologist, Oxford University Hospitals NHS Foundation Trust*
*10 Honorary Lecturer, UCL Division of Surgery and Interventional Science, London, UK*

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**Email**: Charles.oliver@ucl.ac.uk
**Key words**: Anaemia and coagulation; peri-operative management
**Twitter handles:** @DocAShah; @SugavanamAnita; @SimonStanworth; @CMOliver_

**Summary**

Pre-operative anaemia is associated with poor outcomes after elective surgery, but its relationship to outcomes after emergency surgery is unclear. We analysed data from the National Emergency Laparotomy Audit from 1st December 2013 to 30th November 2017, excluding laparotomy for haemorrhage. Anaemia was classified as: 'mild' 129-110 $g.l^{-1}$; 'moderate' 109-80 $g.l^{-1}$; or 'severe' ≤ 79 $g.l^{-1}$. The primary outcome was 90-day mortality. Secondary outcomes were 30-day mortality, return to theatre and postoperative hospital stay. The primary outcome was available for 86,763 patients, of whom 45,306 (52%) were anaemic. There were 12,667 (15%) deaths at 90 postoperative days and 9246 (11%) deaths at 30 postoperative days. Anaemia was associated with increased 90-day and 30-day mortality, odds ratio (95% CI): mild, 1.15 (1.09-1.21); moderate, 1.44 (1.36-1.52); and severe, 1.42 (1.24-1.63), $p < 0.001$ for all; mild, 1.07 (1.00-1.12), $p = 0.030$; moderate, 1.30 (1.21-1.38), $p < 0.001$; and severe, 1.22 (1.05-1.43), $p = 0.010$, respectively. All categories of anaemia were associated with prolonged hospital stay, adjusted coefficient (95% CI): mild, 1.31 (1.01-1.62); moderate, 3.41 (3.04-3.77); severe, 2.80 (1.83-3.77), $p < 0.001$ for all. Moderate and severe anaemia were associated with increased risk of return to theatre, odds ratio (95% CI): moderate 1.13 (1.06-1.21), $p < 0.001$; and severe 1.23 (1.06-1.43), $p < 0.006$. Pre-operative anaemia is common in patients undergoing emergency laparotomy and is associated with increased postoperative mortality and morbidity.

**Commented [A1]:** These have been corrected to match the values in Table 2.

**Introduction**

Approximately 313 million operations are performed worldwide each year, after which at least 4 million (1%) people die within 30 postoperative days, accounting for 8% of all deaths [1, 2]. The rates of postoperative complications and morbidity are even higher [3]. The causes of poor postoperative outcomes are incompletely understood but include pre-existing co-morbidity, systemic inflammation and insufficient oxygen delivery to tissues [4-6]. Adequate oxygen delivery is dependent on cardiac output and arterial oxygen content. Low haemoglobin reduces arterial oxygen content and oxygen delivery for a given cardiac output.

Anaemia before elective surgery is present in 25-40% patients and it is associated with poor postoperative outcomes [7-9]. It remains unclear to what extent this association is causal. Despite this uncertainty, recent consensus statements strongly recommend investigating and treating anaemia before elective surgery, but it is less clear how these recommendations would apply to patients undergoing emergency surgery [10-12].

Approximately 11% of 30,000 patients who have an emergency laparotomy every year in England and Wales die within 30 days, with survivors discharged from hospital on average 15 days later [13, 14]. Patients who have emergency laparotomy are older than the patients who have scheduled laparotomy: they have multiple co-morbidities and they may have concurrent infection, organ dysfunction or cancer, all of which contribute to anaemia [15]. Little is known about the associations between pre-operative anaemia and postoperative outcomes in patients undergoing emergency surgery. We hypothesised that pre-operative anaemia was associated with increased mortality and complications after emergency laparotomy.

**Methods**

We used standard methods to report this secondary analysis of data submitted to the National Emergency Laparotomy Audit (NELA) between 1st December 2013 and 30th November 2017 [16-19]. This analysis was approved by the Health Care Quality Improvement Partnership.

Adults (≥ 18 years) were eligible for inclusion in NELA if they had an expedited, urgent or emergency abdominal procedure on the gastrointestinal tract for conditions such as perforation, obstruction, ischaemia or abdominal abscess. We did not study patients who had laparotomy for acute bleeding or those with missing data. The primary outcome was all-cause mortality within 90 days of the index operation (Office for National Statistics death register). Secondary outcomes were 30-day mortality, return to theatre and postoperative length of stay in an acute hospital (for survivors).

We used the World Health Organization definitions of anaemia for men to categorise pre-operative haemoglobin concentrations for men and women: 'mild', 129-110 $g.l^{-1}$ 'moderate', 109-80 $g.l^{-1}$ and 'severe', ≤ 79 $g.l^{-1}$ [20, 21]. We analysed other pre-operative variables: age; sex; ASA physical status; surgical urgency; ECG abnormalities; cardiac signs; respiratory history; blood concentrations of urea, creatinine, sodium, potassium, white blood cells; heart rate; systolic blood pressure; and Glasgow Coma Scale (GCS) status. We also analysed intra-operative blood loss, peritoneal soiling, malignancy, operative severity, year of operation, number of operations during the index admission, grade of operating surgeon and anaesthetist and whether the patient was directly admitted to a critical care unit postoperatively.

We truncated continuous variables at the 1st and 99th percentile [22]. We log-transformed the skewed distributions of pre-operative serum creatinine and urea, which we then adjusted for non-linearity with a quadratic term that we also used for serum potassium, white blood cell count, heart rate and systolic blood pressure [13]. A fractional polynomial was used to transform the serum sodium distribution [13]. We categorised GCS: 3-8; 9-12; and 13-15.

We did not calculate a sample size for this secondary analysis. We used logistic regression to test the association of pre-operative haemoglobin concentration categories with mortality and return to theatre and linear regression to test their association with acute hospital length of stay. We also analysed haemoglobin values at a single threshold of < 130 $g.l^{-1}$. We then entered all other variables into multivariate models.

We used the area under the receiver-operating characteristic (ROC) curve to calculate the discrimination of death at 30 postoperative days by the NELA model and its calibration with the Hosmer-Lemeshow statistic. We report results for the whole cohort and patients categorised by; year of surgery, from 1st December to 30th November the next year (2013-4, 2014-5, 2015-6, 2016-

7); [haemoglobin], 129-110 $g.l^{-1}$, 109-80 $g.l^{-1}$, $\leq$ 79 $g.l^{-1}$. We used Stata for analyses (Version 15; StataCorp, College Station, Texas, USA).

**Results**

We analysed survival to 90 postoperative days for 86,763/95,844 (91%) patients, of whom 12,667 (14.5%) died (Table 1 and Supplementary Information Fig. S1). We analysed length of hospital stay for 77,389/95,844 (81%) patients.

There were 45,306/86,763 (52%) patients anaemic before laparotomy, with haemoglobin concentrations: 129-110 $g.l^{-1}$ in 24,901 (29%) patients; 109-80 $g.l^{-1}$ in 18,626 (21%) patients; and $\leq$ 79 $g.l^{-1}$ in 1779 (2%) patients (Fig. 1).

Overall 90-day mortality was 12,667 (15%), 8064/45,306 (18%) in anaemic patients. All categories of anaemia were associated with increased 90-day mortality on univariate analysis and these associations remained statistically significant after adjustment (Table 2). Overall 30-day mortality was 9276 (11%), 5681/45,306 (13%) in anaemic patients. All categories of anaemia were associated with increased 30-day mortality on univariate analysis and these associations remained statistically significant after adjustment (Table 3).

The rate of unplanned return to theatre following emergency laparotomy was higher in patients with anaemia across all categories on univariate analysis. These associations remained statistically significant after adjustment only in patients with moderate and severe anaemia (Table 4). Pre-operative anaemia was associated with prolonged postoperative hospital stay when compared to patients without anaemia. These associations remained statistically significant across all categories after adjustment (Table 5).

The discrimination and validation of the NELA risk model are displayed in Table 6 and Figures 2 and 3.

**Discussion**

We found that about half the patients who had emergency laparotomy were anaemic, which was associated with mortality 30 days and 90 days later and unplanned return to theatre and length of hospital stay.

We have completed the first external validation of the NELA risk model, which was derived from 38,830 patients who had an emergency laparotomy between December 2013 and November 2015. The calibration of the model was good calibration across all levels of risk and over time despite changes in the inclusion and exclusion criteria of the NELA dataset.

The association of pre-operative anaemia with adverse clinical outcomes after scheduled surgery has been thoroughly described, but not after unscheduled surgery. A retrospective study reported that 61% of 310,311 US Veterans were anaemic before emergency major noncardiac surgery, but did not report clinical outcomes. Pre-operative anaemia has been associated with increased mortality after repair of hip fracture [24].

It remains unclear if the association of anaemia with poor outcomes is causal or not [25, 26]. We postulate that the association with mortality at 30 postoperative days is more likely to be causative than mortality at 90 days, which we think is likely to be associated with underlying disease. If so, targeted management of anaemia is more likely to reduce morbidity and mortality at 30 days than 90 days.

We think that our findings are likely to be generalisable, at least within the United Kingdom, due to national patient coverage over multiple years with rigorous data collection, linked with externally validated mortality data. We also opted to use contemporary definitions of anaemia in view of recent work suggesting that traditional WHO thresholds may lead to under-diagnosis of anaemia in women [21].

Our study is limited by unidentified factors that may be associated with both pre-operative anaemia and outcomes. We were unable to adjust for peri-operative red blood cell transfusion, which is not recorded by NELA. The haemoglobin concentration at the time of emergency laparotomy is not known as the NELA database does not detail when pre-operative haemoglobin concentration was measured. We did not analyse the association of postoperative haemoglobin concentrations with outcomes as they were not recorded for 25% of the patients. We could not explore the causes anaemia and its varying associations with morbidity and mortality over time. The causes of death were not available to us.

The widespread adoption of restrictive transfusion practices is associated with more patients being discharged anaemic from hospital [27]. Prospective studies, addressing the limitations identified from our work, are already underway [28]. A recent scoping review found evidence of

poor reporting of patient-centred outcomes in anaemia management studies [29], although data are beginning to emerge on the effects of anaemia management on quality of life [30].

There is no consensus on the peri-operative management of anaemic emergency surgery patients, for instance with treatments such as iron and erythropoietin, although haematinics are recommended by some expert panels [11, 12]. There is an uncertain effect of iron transfusions on infection, whilst red blood cell transfusion is associated with harm [31-34]. Newer markers of iron status, such as hepcidin, may help predict which patients will respond to intravenous iron [35-37]. A combination of intravenous iron, erythropoietin, B12 and folic acid given to patients within 24 h of elective cardiac surgery reduced red blood cell transfusion in the first seven postoperative days [38]. This and similar treatments should be investigated in the NELA population.

In conclusion, pre-operative anaemia is common in patients who have an emergency laparotomy and is associated with increased 90-day mortality, unplanned return to theatre and postoperative hospital length of stay. Further research is needed to determine whether investigation and targeted peri-operative treatment of anaemia in this high-risk patient cohort may act to improve outcomes.

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**Table 1** Characteristics of 86,763 patients who had emergency laparotomy, categorised by pre-operative haemoglobin concentration. Values are number (proportion), mean (SD) or median (IQR [range]).

| Variable | Pre-operative [haemoglobin]; $g.l^{-1}$ | | | |
|---|---|---|---|---|
| | **≥ 130 (n = 41,457)** | **129-110 (n = 24,901)** | **109-80 (n = 18,626)** | **≤ 79 (n = 1779)** |
| **Age; years** | 66 (52-76 [18-103]) | 69 (55-79 [18-105]) | 69 (55-78 [18-102]) | 65 (49-75 [18-100]) |
| **Hb; $g.l^{-1}$** | 145 (137-155 [130-250]) | 120 (115-125 [110-129]) | 99 (92-105 [80-109]) | 72 (68-74 [40-79]) |
| **Male** | 22,898 (55%) | 9895 (40%) | 7882 (42%) | 831 (47%) |
| **ASA*** | | | | |
| **1** | 5861 (14% | 1951 (8%) | 876 (5%) | 99 (6%) |
| **2** | 16,343 (39%) | 8802 (36%) | 5057 (27%) | 420 (24%) |
| **3** | 13,002 (31%) | 9617 (39%) | 7833 (42%) | 628 (35%) |
| **4** | 5638 (14%) | 4189 (17%) | 4379 (24%) | 547 (31%) |
| **5** | 613 (2%) | 342 (1%) | 481 (3%) | 85 (5) |
| **Both consultants in theatre** | 28,447 (69%) | 18,404 (74%) | 14,358 (77%) | 1429 (80%) |
| **Return to theatre** | 3027 (7%) | 1966 (8%) | 2022 (11%) | 250 (14%) |
| | | | | |
| **Mortality** | | | | |
| **30 days** | | | | |
| **Observed** | 3595 (9%) | 2596 (10%) | 2767 (15%) | 318 (18%) |
| **Predicted** | 9% | 11% | 13% | 16% |
| **90 days** | | | | |
| **Observed** | 4603 (11%) | 3677 (15%) | 3953 (21%) | 434 (24%) |
| **~~Predicted~~** | ? | ? | ? | ? |
| | | | | |
| **Days in hospital** | **n = 38,119** | **n = 22,333** | **n = 15,552** | **n = 1385** |
| | 10 (6-17 [1-421]) | 12 (7-20 [1-584]) | 15 (9-26 [1-446]) | 15 (9-28 [2-220]) |

ASA, ASA physical status; Hb, haemoglobin.

*Values may not sum to 100% due to rounding

**Table 2** Odds ratios (95% CI) for the associations of pre-operative and intra-operative variables with 12,667 deaths within 90 days of emergency laparotomy in 86,763 patients.

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | p value | OR | p value |
| **Pre-operative** | | | | |
| **Haemoglobin; g.l$^{-1}$** | | | | |
| **> 129** | Reference | | Reference | |
| **110-129** | 1.38 (1.32-1.45) | < 0.001 | 1.15 (1.09-1.21) | < 0.001 |
| **80-109** | 2.15 (2.05-2.26) | < 0.001 | 1.44 (1.36-1.52) | < 0.001 |
| **≤ 79** | 2.58 (2.31-2.89) | < 0.001 | 1.42 (1.24-1.63) | < 0.001 |
| **Age** | 1.04 (1.04-1.05) | < 0.001 | 1.04 (1.03-1.04) | < 0.001 |
| **Female** | 0.99 (0.95-1.03) | 0.281 | 1.02 (0.97-1.07) | 0.48 |
| **ASA** | | | | |
| **1-2** | Reference | | Reference | |
| **3** | 4.15 (3.91-4.41) | < 0.001 | 2.06 (1.93-2.20) | < 0.001 |
| **4** | 14.4 (13.6-15.3) | < 0.001 | 4.06 (3.77-4.38) | < 0.001 |
| **5** | 46.5 (41.3-52.3) | < 0.001 | 8.43 (7.32-9.71) | < 0.001 |
| **Urgency of surgery; h** | | | | |
| **18-24** | Reference | | Reference | |
| **6-18** | 0.87 (0.82-0.93) | < 0.001 | 0.85 (0.79-0.92) | < 0.001 |
| **2-6** | 1.36 (1.28-1.45) | < 0.001 | 0.97 (0.89-1.04) | < 0.001 |
| **< 2** | 3.43 (3.21-3.67) | < 0.001 | 1.42 (1.29-1.55) | < 0.001 |
| **ECG** | | | | |
| **No abnormalities** | Reference | | Reference | |
| **AF rate 60-90** | 2.44 (2.25-2.64) | < 0.001 | 1.19 (1.09-1.31) | < 0.001 |
| **Other** | 3.11 (2.97-3.25) | < 0.001 | 1.14 (1.08-1.21) | < 0.001 |
| **Cardiac sign** | | | | |
| **Normal** | Reference | | Reference | |
| **Anti-hypertensive therapy** | 2.20 (2.10-2.29) | < 0.001 | 1.02 (0.97-1.08) | 0.38 |
| **Borderline cardiomegaly** | 4.13 (3.85-4.42) | < 0.001 | 1.26 (1.15-1.37) | < 0.001 |
| **Cardiomegaly** | 5.57 (4.90-6.32) | < 0.001 | 1.26 (1.08-1.46) | 0.003 |
| **Heart rate** | 1.02 (1.02-1.02) | < 0.001 | 1.01 (1.00-1.01) | < 0.001 |
| **Systolic blood pressure** | 0.98 (0.98-0.98) | < 0.001 | 0.99 (0.99-1.00) | < 0.001 |
| **Respiratory** | | | | |
| **No dyspnoea** | Reference | | Reference | |
| **Dyspnoea on exertion** | 2.46 (2.32-2.58) | < 0.001 | 1.29 (1.22-1.37) | < 0.001 |
| **Dyspnoea < one stair flight** | 3.87 (3.66-4.10) | < 0.001 | 1.58 (1.47-1.69) | < 0.001 |
| **Dyspnoea at rest** | 5.64 (5.21-6.11) | < 0.001 | 1.65 (1.49-1.82) | < 0.001 |
| **Blood results** | | | | |
| **Creatinine** | 2.82 (2.72-2.93) | < 0.001 | 1.27 (1.20-1.35) | < 0.001 |
| **Sodium** | 1.00 (0.99-1.00) | 0.422 | 1.00 (1.00-1.01) | < 0.001 |
| **Potassium** | 1.38 (1.34-1.43) | < 0.001 | 1.21 (1.16-1.25) | < 0.001 |
| **Urea** | 2.68 (2.60-2.76) | < 0.001 | 1.38 (1.32-1.46) | < 0.001 |
| **White blood cell count** | 1.02 (1.02-1.03) | < 0.001 | 1.00 (0.99-1.00) | 0.54 |
| **Glasgow Coma Score** | | | | |
| **13-15** | Reference | | Reference | |
| **9-12** | 5.88 (5.02-6.90) | < 0.001 | 1.84 (1.51-2.22) | < 0.001 |
| **3-8** | 7.76 (6.98-8.62) | < 0.001 | 2.23 (1.96-2.54) | < 0.001 |
| **Intra-operative** | | | | |
| **Peritoneal soiling** | | | | |

| | | | | |
|---|---|---|---|---|
| **None** | Reference | | Reference | |
| **Serous fluid** | 1.38 (1.31-1.45) | < 0.001 | 1.10 (1.03-1.16) | 0.001 |
| **Localised pus** | 0.82 (0.75-0.88) | < 0.001 | 0.89 (0.81-0.98) | 0.012 |
| **Pus, blood or bowel content** | 2.10 (2.00-2.20) | < 0.001 | 1.33 (1.25-1.42) | < 0.001 |
| **Blood loss; ml** | | | | |
| **<100** | Reference | | Reference | |
| **101-500** | 1.29 (1.24-1.35) | < 0.001 | 1.05 (1.00-1.10) | 0.074 |
| **501-1000** | 1.75 (1.61-1.92) | < 0.001 | 1.15 (1.03-1.27) | 0.010 |
| **>1000** | 2.79 (2.42-3.23) | < 0.001 | 1.85 (1.54-2.21) | < 0.001 |
| **Malignancy status** | | | | |
| **None** | Reference | | Reference | |
| **Primary only** | 1.06 (0.99-1.13) | 0.063 | 1.31 (1.22-1.41) | < 0.001 |
| **Nodal metastases** | 1.66 (1.53-1.80) | < 0.001 | 2.43 (2.20-2.69) | < 0.001 |
| **Distant metastases** | 3.97 (3.75-4.20) | < 0.001 | 6.45 (6.02-6.92) | < 0.001 |
| **Consultant in theatre** | | | | |
| **Surgeon** | 1.37 (1.28-1.46) | < 0.001 | 1.06 (0.98-1.14) | 0.094 |
| **Anaesthetist** | 1.59 (1.51-1.68) | < 0.001 | 1.03 (0.97-1.09) | 0.29 |
| **ICU admission from theatre** | 3.06 (2.91-3.20) | < 0.001 | 1.05 (0.99-1.11) | 0.088 |

AF, Atrial Fibrillation; ASA, ASA physical status; COAD, chronic obstructive airways disease; ICU, intensive care unit.

**Table 3** Odds ratios (95% CI) for the associations of pre-operative anaemia with 9276 deaths within 30 days of emergency laparotomy in 86,763 patients.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **OR (95%CI)** | **p value** | **OR (95%CI)** | **p value** |
| **Haemoglobin; g.l$^{-1}$** | | | | |
| **> 129** | Reference | | Reference | |
| **110-129** | 1.22 (1.16-1.29) | < 0.001 | 1.07 (1.00-1.12) | 0.030 |
| **80-109** | 1.83 (1.74-1.94) | < 0.001 | 1.30 (1.21-1.38) | < 0.001 |
| **≤ 79** | 2.29 (2.02-2.60) | < 0.001 | 1.22 (1.05-1.43) | 0.010 |

**Table 4** Odds ratios (95% CI) for the associations of pre-operative anaemia with return to theatre after emergency laparotomy in 86,763 patients .

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **OR (95%CI)** | **p value** | **OR (95%CI)** | **p value** |
| **Haemoglobin; g.l$^{-1}$** | | | | |
| **> 129** | Reference | | Reference | |
| **110-129** | 1.09 (1.02-1.15) | 0.004 | 1.02 (0.96-1.09) | 0.472 |
| **80-109** | 1.55 (1.46-1.65) | < 0.001 | 1.13 (1.06-1.21) | < 0.001 |
| **≤ 79** | 2.10 (1.83-2.42) | < 0.001 | 1.23 (1.06-1.43) | < 0.006 |

**Table 5** Linear regression for the associations of pre-operative anaemia with hospital stay after emergency laparotomy in 86,763 patients

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **Coefficient (95%CI)** | **p value** | **Coefficient (95%CI)** | **p value** |
| **Haemoglobin; g.l$^{-1}$** | | | | |
| **> 129** | Reference | | Reference | |
| **110-129** | 2.57 (2.25-2.89) | < 0.001 | 1.31 (1.01-1.62) | < 0.001 |
| **80-109** | 6.65 (6.29-7.01) | < 0.001 | 3.41 (3.04-3.77) | < 0.001 |
| **≤ 79** | 7.87 (6.83-8.90) | < 0.001 | 2.80 (1.83-3.77) | < 0.001 |

**Table 6** Validation of the National Emergency Laparotomy Audit risk model

Commented [A2]: Alterative

| Study group | Discrimination | Calibration |
|---|---|---|
| **Whole study cohort** | 0.863 | 71.6 |
| **Year of NELA** | | |
| **2013-4** | 0.861 | 23.3 |
| **2014-5** | 0.867 | 29.1 |
| **2015-6** | 0.856 | 21.8 |
| **2016-7** | 0.863 | 33.0 |
| **Haemoglobin; $g.l^{-1}$** | | |
| **> 129** | 0.880 | 57.1 |
| **110-129** | 0.851 | 20.5 |
| **80-109** | 0.836 | 61.4 |
| **≤ 79** | 0.826 | 25.4 |

**Figure 1** Histogram representing distribution of pre-operative haemoglobin in patients undergoing emergency laparotomy.

**Figure 2** Receiver operator characteristic curve of the NELA risk tool versus 30-day mortality.

**Figure 3** Giviti calibration belt comparing the observed 30-day mortality (vertical axis) against the predicted NELA risk tool mortality (horizontal axis). Predicted rates calibrated well with observed rates. The red line is the unitary tangent, the light grey are 95% CI and the dark grey are 99% CI.

**Supplementary Figure 1** STROBE flow diagram of patients included and excluded from analysis.