Quality of life measures predict mortality in patients with cirrhosis and severe ascites

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SM contributed to study design, data analysis, and drafting and revision of the manuscript. PJ contributed to study design, data analysis, and drafting and revision of the manuscript. HW contributed to study design, data collection and analysis, and revision of the manuscript. LA contributed to data analysis and revision of the manuscript. HV contributed to study design, data analysis, and revision of the manuscript. RJ contributed to study design, data analysis, and drafting and revision of the manuscript.

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Abbreviations:

HCC, hepatocellular carcinoma; HRQL, health related quality of life; HRS, hepatorenal syndrome; INR, international normalised ratio; IQR, interquartile range; LVP, large volume paracentesis; MCS, mental component score; MELD score, model for end-stage liver disease score; PCS, physical component score; SF-36, the medical outcomes study short form-36; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

Abstract

Background: Severe ascites (difficult-to-treat or refractory ascites) is associated with both a poor health-related quality of life (HRQL) and a mortality in excess of that captured by current prognostic clinical scores.

Aim: To determine the association between HRQL and mortality in patients with severe ascites.

Methods: The data were retrospectively evaluated from previously published multi-centre randomised controlled trials examining the efficacy of satavaptan in patients with ascites.

Results: Of the 496 patients randomised who completed the SF-36 HRQL tool, 405 patients had complete datasets and were included in the analysis [difficult-to-treat ascites, n=164 (≥ 2 large volume paracentesis in 3-months prior to enrolment) or refractory ascites, n=241]. Overall, patients reported poor HRQL, in particular the physical component score (PCS) of SF-36. The physical component score (PCS) correlated with the mental component score (MCS) of SF-36 (Spearman rank correlation=0.68) but not with markers of severity of liver disease. PCS, but not MCS, was significantly lower in patients who died (p=0.01 and p=0.84 respectively). After confounder-adjustment, the hazard ratio for a 10-point increase in the PCS was 0.83 (95% CI 0.72 to 0.97) for all-cause mortality and 0.84 (95% CI 0.71 to 0.99) for cirrhosis-related deaths only, indicating that patients with better physical HRQL live longer on average.

Conclusions: Poor physical component score (PCS) of SF-36 is an independent predictor of 12-month mortality in patients with severe ascites independent of current

prognostic clinical scores and as such holds promise not only in prognostic modelling but as an end point in evaluation of therapies targeting ascites.

Introduction

Ascites is a frequent complication of cirrhotic liver disease with 60% of patients developing ascites within 10 years of diagnosis (1). The presence of diuretic refractory ascites has been associated with increased mortality (2)(3). It is, however, not a component of the current model for end-stage liver disease (MELD) based risk scores (4)(5). Excess mortality in patients with hard-to-treat or refractory ascites in comparison to those without demonstrated that the risk of mortality persisted despite adjustment for MELD score (6)(7).

Commented [PJ1]: Is this a different concept from "difficult-to-treat"? If not, we had better stick to one term.

Health related quality of life (HRQL) has been shown to be a predictor of mortality in a broad range of chronic medical conditions (8)(9)(10)(11)(12)(13)(14)(15)(16)(17) as well as in patients on the liver transplant waiting list (18). A reduced HRQL was demonstrated to be independent of the conventional clinical scores such as the MELD score in predicting mortality (20). The Medical Outcomes Study Short Form-36 (SF-36) is probably the most widely used generic health-related quality of life tool both in the general population and in chronic liver disease (20)(21). The SF-36 questionnaire includes 36 questions composed of 8 multi-item scales (22), which reflect the impact of health problems on both the physical and mental condition of the patient. A greater score reflects better quality of life. Two summary sub-scores can be calculated which are weighted combinations of the eight scales, one to reflect the

impact on physical function physical component score (PCS) and one to reflect the impact on psychological function mental component score (MCS)(22).

Refractory ascites has been well documented to be associated with an impairment in HRQL (23)(24)(25)(26) but whether this is associated with the prognosis of this group of patients is unknown. The aims of this study were to determine the association between HRQL, using the SF-36, and mortality in patients with severe ascites.

Methods

Patients

Between July 2006 and December 2008 a multicentre randomised controlled trial was conducted to examine the efficacy of satavaptan in treating ascites in patients with cirrhosis (27). Patients included in this study were those with ascites managed with a combination of diuretics and therapeutic paracentesis. At the time of inclusion all of these patients completed the SF-36 questionnaire and it is this data that was used for the analysis presented.

The trial excluded patients with variceal bleeding or SBP in the 10 days before randomisation and patients with a functional transjugular intrahepatic portosystemic shunt (TIPS). Other reasons for exclusion were: serum creatinine >150 µmol/L, serum potassium <3.5 or >5.0 mmol/L, serum sodium >143 mmol/L, serum bilirubin >150 µmol/L, serum magnesium <0.65 mmol/l, INR >3.0, platelets <30,000/mm^3, neutrophils <1,000/mm^3, systolic arterial pressure <80 mmHg or symptomatic orthostatic hypotension, hepatocellular carcinoma (HCC) exceeding the Milan criteria, use of a potent modifier of the cytochrome P450 3A pathway, positive hepatitis B virus infection, previous liver transplantation, hepatic encephalopathy, gastrointestinal bleeding, ascites of cardiac origin or due to peritoneal infection (e.g. tuberculosis) or peritoneal carcinoma, previous exposure to satavaptan, positive pregnancy test, Budd Chiari syndrome or use of drugs that increase the risk of Q-T interval prolongation.

Additional patients were excluded from our study: those with incomplete data on SF-36, those with missing data for INR, bilirubin, creatinine, sodium, or albumin, and

those who were hospitalized or had an infection at the time of randomisation. The planned treatment duration was 52 weeks with an additional safety visit 1-2 weeks later, but the trial was stopped early due to an increased mortality among one of the treatment groups. Nonetheless, patients were contacted shortly after week 52 of planned treatment to determine survival or date of death.

Data collection

The SF-36 questionnaire was completed by the patients at the time of inclusion in the study. Additional data including creatinine, INR, bilirubin, sodium, albumin, ascites severity, history of variceal bleeding, history of SBP, and history of HCC were collected at the same time. Patients were classified as difficult-to-treat or refractory by the managing clinician at each participating centre at the time of enrolment using the following definitions.

Difficult-to-treat ascites: patients with recurrent ascites having received a large volume paracentesis (LVP) of at least 4 litres in the 24 hours before randomisation and with a history of at least one other LVP in the previous 3-months. All patients were receiving a sodium-restricted diet and one or more diuretic agents.

Refractory ascites: patients with recurrent ascites having a LVP of at least 4 litres less than 24 hours before randomisation and a history of at least one other LVP in the previous 3 months. Additionally patients were receiving a sodium-restricted diet but were unsuitable for treatment with diuretic agents. In another word, “refractory

ascites" includes patients with intractable ascites which are "unsuitable to treatment with diuretic agents".

Statistical analysis

Follow-up started at randomisation and ended at death or in censoring at the time of the last patient contact after week 52. Data were evaluated retrospectively. We used the Spearman rank correlation to measure correlation between variables. We used the Kaplan-Meier estimator to compute cumulative mortality risks for two groups defined by halves of the physical component score. To control for confounding variables we used Cox proportional hazards regression. The Cox model estimated the effects of a 10-point increase in the physical or mental component scores on the all-cause mortality hazard adjusted for confounding by patient gender, age, creatinine, INR, bilirubin, sodium, albumin, ascites severity (difficult-to-treat or refractory), history of variceal bleeding, history of SBP, and history of HCC.

The clinical team looking after the patients determined the cause of death. We categorized all deaths as either cirrhosis-related (liver failure, HCC, gastrointestinal bleeding, hepatorenal syndrome, or infection) or from other, including unknown, causes, and we then examined the association between the physical and mental component scores and the hazard of cirrhosis-related death. In this analysis we used the same regression model and adjusted for the same confounders as in the primary analysis.

Results

Patients

Of the 496 patients enrolled in the original study, 91 were excluded from our analysis: 69 patients with incomplete SF-36 data; 4 patients with incomplete biochemical data (INR, bilirubin, creatinine, sodium, or albumin); 12 patients were hospital inpatients and 6 patients had an active infection at the time of randomisation (Figure 1). All patients had either difficult-to-treat ascites (n=164) or refractory ascites (n=241) (table 1). As no significant differences were seen in SF-36 physical and mental components scores (PCS and MCS) and mortality between the difficult-to-treat and the refractory ascites groups (table 1) all patients were combined for the subsequent analyses. Table 2 shows the summary of the cirrhosis related complications observed in study period for patients with difficult to treat and refractory ascites.

SF36 and subscales in study population

Patients' physical and mental components scores (PCS and MCS) were correlated so that patients with poor quality of life in the physical domain also had poor quality of life in the mental domain (Spearman rank correlation = 0.68). Neither the physical (PCS) nor the mental (MCS) component scores correlated significantly with other patient characteristics (Figure 2). The physical and mental components scores (PCS and MCS) were similar in those randomised to satavaptan or placebo. Specifically, the median PCS was 39 (IQR 28–56) in those randomised to satavaptan vs. 40 (IQR 28–50) in those randomised to placebo [Spearman rank correlation: 0.01]. The

median MCS were 53 (IQR 35–73) and 48 (IQR 33–70), respectively, [Spearman rank correlation: 0.04].

The distribution of the eight SF-36 components is shown in Figure 3. Patients scored poorly in the 'role physical' component in which 61% of patients scored 0 points, and 15% scored 25 points. The other components of the physical component scores (PCS) were more evenly distributed. Patients' physical component scores (PCS) ranged from 4 to 94 with a median of 39 (IQR 28–52). As for the mental component score (MCS), the distribution of the 'role emotional' component was striking: 37% of patients scored 0 points, 16% scored 33 points, 0.3% scored 50 points, 11% scored 67 points, and 37% scored 100 points (Figure 3). The patients' mental component score (MCS) ranged from 5 to 99 with a median of 51 (IQR 35–71). When examining the associations between PCS/MCS and leg oedema, we found that patients who did not have leg oedema had better HRQoL, which was statistically significant in both physical and mental components scores (PCS and MCS) domains (Figure 4) regardless of the severity of oedema. There was no significant association between the presence of oedema and survival.

Mortality and morbidity

During 324.7 total years of follow-up, 99 deaths occurred. The median physical component score (PCS) was 34 (IQR 24-49) for those who died, which was significantly lower compared to those who survived during the follow up period whose median physical component score (PCS) was 41 (IQR 29-53). No statistically significant difference was seen in the MCS between those who survived the follow

up period and those who did not. Interestingly, the median values in the mental component score (MCS) variables ”role emotional” and ”social function” were higher in patients that died compared to those that survived. As no overall difference in mental component score (MCS) was demonstrated, we focused on the role of the physical component score (PCS) for further analyses.

A good quality of life in the physical domain predicted lower risk of death, as indicated by the lower cumulative mortality for patients with above-median physical component score than for patients with below-median score (Figure 5). These observations remained after adjustment for confounding variables. Before confounder adjustment, the hazard ratio for a 10-point increase in the physical component score (PCS) was 0.87 (95% CI 0.78 to 0.97), and after adjustment it was 0.83 (95% CI 0.72 to 0.97) (Table 3). All four individual components were associated with an adjusted hazard ratio below one, but none of them were statistically significant (Table 3).

Satavaptan did not have a specific effect on the HRQoL that determined mortality. The median physical component score (PCS) was 39 (IQR 28-56) for those who had satavaptan vs. physical component score (PCS) of 40 (IQR 28–50) for patients who had placebo. Adding satavaptan as a confounder marginally increased the hazard ratio for PCS to 0.84 (0.71–0.99).

The findings remained essentially unchanged when mortality was restricted to cirrhosis-related deaths only. There were 77 cirrhosis-related deaths during the study period. With confounder-adjustment, the effect of a 10-point increase in the physical

component score (PCS) on the hazard ratio of cirrhosis-related death was 0.84 (95% CI 0.71 to 0.99).

Discussion

Current prognostic scores for patients with advanced liver disease do not identify the risk of these patients with severe ascites accurately as most of them will have a relatively low MELD. It is unclear what does the HRQL is as an end point in clinical trials mean. The study supports the hypothesis that patients with severe ascites have a poor HRQL. Furthermore, HRQL may be more relevant to assess as it also impacts on the survival. Interestingly, the data also demonstrates that patients with difficult-to-treat ascites (managed with combination of diuretics and therapeutic paracentesis) have a similar HRQL and mortality over 1-year as patients classified as having refractory ascites suggesting that nomenclature defining 'refractory ascites' may need to be broadened.

This study offers clear evidence that the presence of severe ascites has a marked impact on a patient's HRQL. About 61% of patients scored 0 on the 'role physical' parameter with a further 15% scoring only 25 points. This describes the impact that severe ascites has on the day-to-day life of patients and also emphasises the unmet need for new therapies in this patient group (28)(29)(30). Compared with repeated large volume paracentesis, HRQL in this group of patients was shown to be improved with interventions to control ascites such as alfapump insertion (31)(32)(33) and transjugular intrahepatic portosystemic shunt (TIPS) insertion (34)(35)(36). Given the relatively low MELD scores, patients with severe ascites receive a relatively low priority on the liver transplant waiting list. Our data may allow development of improved criteria, based on HRQL, to assess patients with severe ascites.

An interesting observation was that, whilst there was no significant difference between the mental component score (MCS) in patients who survived the follow up period and those that did not, the median values in the mental component score (MCS) variables ”role emotional” and ”social function” were higher in patients that died compared to those that survived. The explanation for this observation is not clear from the data collected but was not related to the presence of hepatic encephalopathy or aetiology of liver disease. Alternatively, it may indicate that SF-36 mental component score (MCS) does not reliably assess the HRQL in patients with severe ascites. Patients who died during the follow up period had lower physical component score (PCS) scores than those who survived and the use of Cox proportional hazards regression demonstrated the clear increase in mortality associated with a decreasing PCS. Whilst the physical component score (PCS) correlated with the mental component score (MCS), neither score correlated with the standard variables used to define risk of death in cirrhosis (INR, bilirubin, creatinine, sodium, albumin and age). This observation argues that poor physical HRQL is an independent risk factor for mortality in patients with severe ascites. It also additionally suggests that the physical component score (PCS) may be a potential surrogate end-point for clinical trials in patients with severe ascites, however, this will require the development of an ascites-specific HRQL questionnaire.

The diagnosis of refractory ascites is a critical event in determining the mortality of patients with cirrhosis and defines extremely poor prognosis leading to clinical decisions about insertion of a transjugular intrahepatic porto-systemic shunt or alfapump or liver transplantation. The data from this study suggests that patients who have severe ascites but do not fulfil criteria for refractory ascites also have a poor HRQL and similar risk of mortality as those fulfilling the criteria for refractory

ascites. The data therefore argues for the relaxing the definition of refractory ascites (37). With further validation, new definitions and changed treatment algorithms may emerge.

Our study showed that the quality of life of patients without oedema is marginally better, regardless of the severity of oedema. The associations between physical (PCS) or mental (MCS) components scores and oedema were statistically significant. There was no association with survival. The association of oedema with QoL in patients with ascites has only been reported in a few studies (24). Our findings support the fact that the presence of oedema in patient with ascites is associated with poor quality of life without a significant association with mortality.

In this study we did not include patients who had TIPS or liver transplantation. In the event of LTX or TIPS, the patient concerned had to be withdrawn from the original trials as it was no longer relevant to continue evaluating the effect of satavaptan on ascites. TIPS may have an influence on both, HRQL and survival. Therefore more studies will be needed to explore whether assessment of HRQL may have an influence on the TIPS-indication and post-TIPS survival.

Our study is drawn from the three phase III trials to address the role of HRQL in determining the patient's prognosis. This is different from other studies (24) that analysed the HRQL baseline data from phase II trials of satavaptan in ascites (38)(39)(40)(41) and focused primarily on the clinical factors that are associated with quality of life scores.

SF36 is a standardised generic HRQL measure that has been validated and used in patients with liver disease (20)(20)(21). It is known that there is an association of

both pruritis and muscle cramps with HRQL in cirrhosis (23). SF36 does not capture these symptoms in the study but we assume that SF36 partly reflects presence of these symptoms. Therefore, an ascites specific questionnaire needs to be developed and validated. The subjectivity of any HRQL is possible but we have shown that HRQL, in general, must be considered in the development of mortality prediction models.

The study excluded patients with advanced chronic kidney disease (CKD) from the RCTs. This may limit the ability to generalize our findings to patients outside our specific study population.

In conclusion, this study demonstrates for the first time that HRQL (the physical component score of the SF-36 HRQL tool) predicts mortality in patients with difficult-to-treat and refractory ascites and this is independent of currently used clinical scores. Whilst this suggests that HRQL is an important end point for future therapies targeting the management of ascites, it also argues that further studies are required to develop an ascites-specific HRQL-based clinical score to improve prognostication in this group.

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Figure Legends

Figure 1. CONSORT diagram for patients included in study.

Figure 2. Scatterplot matrix showing correlations between continuous variables in all patients. The lower half shows scatterplots of all two-way combinations of the variables, and the upper half shows the associated Spearman rank coefficients. The physical component score (PCS) and the mental component score (MCS) are the most strongly correlated variables (coefficient = 0.68).

Figure 3. Distribution of the SF-36 questionnaire's 8 components in all patients. Each distribution is shown by a 'violin plot' that shows the median (white dot), the IQR (thick black vertical line), the range (thin black vertical line), and a smoothed histogram-like representation of the actual measurements.

Figure 4. The associations between PCS/MCS and leg oedema.

Figure 5. Cumulative all-cause mortality for all patients defined by below- or above-median physical component score (PCS).

Tables:

Table 1. Characteristics of the 405 patients included in the study subdivided by difficult-to treat or refractory ascites.

Baseline characteristic	Difficult to treat ascites	Refractory ascites	P value
Age (years)	58 (51–65)	58 (51–66)	0.78
Male (n, %)	113 (69%)	181 (75%)	0.17
Etiology (n, %)			0.04
Alcohol only	106 (65%)	165 (68%)	
HCV only	14 (9%)	21 (9%)	
Alcohol + HCV	8 (5%)	24 (10%)	
Other	36 (22%)	31 (13%)	
History of GI bleeding (n, %)	29 (18%)	53 (22%)	0.29
History of SBP (n,%)	28 (17%)	40 (17%)	0.90
History of HCC (n,%)	5 (3%)	11 (5%)	0.44
Laboratory values			
Bilirubin (mg/dL)	26 (16–43)	28 (17–40)	0.73
INR	1.4 (1.3–1.6)	1.4 (1.2–1.6)	0.78
Albumin (g/dL)	33 (29–37)	34 (30–38)	0.51
Creatinine (mg/dL)	80 (65–98)	81 (65–103)	0.52
Sodium (mmol/L)	136 (134–139)	136 (134–139)	0.98
Platelets ($x10^9$/L)	133 (99-189)	140 (101-195)	0.44
WBC ($x10^9$/L)	5.6 (4.3-7.7)	5.8 (4.4-7.1)	0.89

CRP (mg/L)	N/A	N/A	
MELD	14 (11-17)	14 (11-18)	0.42
CP score (median, IQR)	8 (8-9)	8 (8-10)	0.20
1 year mortality (%)	22% (16-29)	29% (23-35)	0.17
HRQL - SF36 sub-scores			
Physical component score, median (IQR)	39 (26–52)	39 (28–52)	0.67
Physical function, median (IQR)	50 (30–70)	45 (30–67)	0.66
Role physical, median (IQR)	0 (0–25)	0 (0–50)	0.12
Bodily pain, median (IQR)	61 (31–74)	52 (31–80)	0.70
General health, median (IQR)	39 (25–52)	40 (30–55)	0.26
Mental component score, median (IQR)	49 (32–70)	53 (35–71)	0.45
Social function, median (IQR)	50 (38–75)	63 (38–75)	0.23
Role emotional, median (IQR)	33 (0–100)	33 (0–100)	0.85
Vitality, median (IQR)	40 (25–55)	40 (30–55)	0.74
Mental health, median (IQR)	62 (44–76)	60 (48–76)	0.63

Data are mean ± SD or median (Q1-Q3). For continuous variables, the p-value is from a Spearman rank correlation test of independence. For categorical variables, the p-value is from a chi-square test of independence. For 1-year mortality, the p-value is from a logrank test of independence.

Table 2. Complications observed in study period subdivided by difficult to treat or refractory ascites.

	Difficult to treat ascites	**Refractory ascites**
Paracenteses (median, IQR)	5 (2-10)	7 (2-13)
Total volume of ascites removed (litres, median IQR)	29 (9-60)	43 (14-76)
SBP (number % of patients with ≥1 episode among patients with no previous SBP episodes)	13 (10)	24 (12)
Any infection (number % of patients with ≥1 infection)	51 (31)	83 (34)
Variceal haemorrhage (number % of patients with ≥1 bleeding among patients with no previous bleeding)	5 (4)	13 (7)
Hepatic Encephalopathy (number % patients with ≥1 episode of HE grade ≥1)	50 (30%)	75 (31%)
Hepatic Encephalopathy (number % patients with ≥1 episode of HE grade ≥2)	35 (21%)	47 (20%)

Liver transplant	2 (1.2)	4 (1.7)
TIPS	1 (0.5)	2 (1.0)
Death	34 (21)	65 (27)

Data are number (%), no significant differences were seen between the groups.

Table 3. Confounder-adjusted effects of physical and mental component scores on the hazard rate of death from any cause.

	Adjusted hazard ratio
Physical component score, per 10 points increase	0.83 (0.72–0.97)
Physical function, per 10 points increase	0.99 (0.89–1.10)
Role physical, per 10 points increase	0.91 (0.82–1.00)
Bodily pain	0.96 (0.87–1.06)
General health	0.98 (0.84–1.15)
Mental component score, per 10 points increase	1.08 (0.96–1.22)
Men vs. women	1.14 (0.70–1.86)
Age, per 10 years increase	1.41 (1.14–1.74)
Creatinine, per 10 µmol/L increase	1.04 (0.97–1.12)
INR, per 1 point increase	1.05 (0.58–1.90)
Bilirubin, per 10 µmol/L increase	1.16 (1.09–1.24)
Sodium, per 10 mmol/L increase	0.42 (0.26–0.68)
Albumin, per 10 g/L increase	0.82 (0.55–1.22)
Refractory vs. diuretic-responsive ascites	1.24 (0.81–1.90)
History of variceal bleeding, yes vs. no	1.20 (0.76–1.90)
History of SBP, yes vs. no	1.83 (1.16–2.90)
History of HCC, yes vs. no	2.61 (1.30–5.23)