

Cirrhotics Treated In Intensive Care Unit Have High Short Term Survival in the Absence of Extrahepatic Organ Dysfunction

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ABSTRACT

AIM: This retrospective study of 85 cirrhotics aimed to identify variables during the first 24 hours of intensive care unit (ICU) admission predicting mortality up to 30 days of hospital discharge, and to analyse the prognostic accuracy of common severity scores in predicting mortality.

MATERIALS AND METHODS: Eighty-five patients with liver cirrhosis admitted to ICU at the Royal Hobart Hospital, a regional Australian center, from 2007 to 2013 inclusive were identified using International Classification of Disease coding and data extracted from medical records. Predictors of mortality were determined via logistic regression and the prognostic accuracy of 5 severity scores calculated by their area under the receiver-operating curve. These included 2 scores commonly used in liver disease; Child Pugh and Model for End-Stage Liver Disease (MELD); as well as 3 scores designed in the intensive care setting: Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology (SAPS II) and Acute Physiology and Chronic Health Evaluation (APACHE II).

RESULTS: Significant variables predicting short-term mortality included infection (excluding spontaneous bacterial peritonitis), requirement for inotropes or mechanical ventilation, elevated

creatinine, decreased Glasgow Coma Scale, decreased pH and elevated white cell count. However the presence of cirrhosis-specific complications such as hepatic encephalopathy, variceal bleeding and spontaneous bacterial peritonitis did not predict mortality and liver-specific prognostic severity scores (Child Pugh and MELD) performed more poorly than the other severity scores designed for the ICU setting.

CONCLUSIONS: ICU admission for cirrhotics should not be deemed futile in the presence of hepatic dysfunction alone; cardiorespiratory, neurological and renal dysfunction should be taken into account. ICU-specific severity scores better prognosticate short-term mortality compared to liver-specific scores.

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Key Words: Cirrhosis, Intensive care; Prognosis; Infection; Acute renal failure; Rural health; Health resources

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INTRODUCTION

Mortality from liver cirrhosis has risen by 33% from 1990 to 2010 and is an increasing economic burden worldwide^[1]. Cirrhotic patients who are admitted to intensive care units (ICU) have historically had high rates of mortality, with over 50% in-hospital mortality in previous studies^[2,3]. The presence of cirrhosis has been found to be an independent predictor of poor survival^[4]. As such, optimal allocation of scarce ICU resources depends on accurate prognostication of such patients as the decision to allocate such resources to cirrhotics is often called into question^[5,6]. It is important for clinicians to have objective

measures that help identify cirrhotic patients who would most benefit from ICU admission, as well as those in whom such measures may be futile. Most studies of cirrhotic patients' survival after ICU have been conducted in centers with specialisation in liver disease^[7], and/or liver transplantation^[8] and thereby may yield findings not applicable to a general hospital setting^[9].

The primary aims of this study were therefore to identify clinical variables during the first 24 hours of ICU admission, in a non-transplant regional center, among a cirrhotic population that predicted mortality up to 30 days after discharge from hospital. A secondary aim was to analyse the prognostic accuracy of common severity scores in predicting mortality. Earlier studies have demonstrated ICU-specific scores to be more accurate in cirrhotics than other liver-specific scores and this study analyses if this applies in the context of a regional ICU.

METHODS

The records of all patients with cirrhosis admitted to the ICU of the Royal Hobart Hospital from 01/01/2007 to 31/12/2013 based on International Classification of Diseases (ICD-10) coding were accessed via electronic hospital databases. The only inclusion criterion was a diagnosis of cirrhosis prior to ICU admission on imaging and/or liver biopsy. This ICU has 20 beds and services the southern part of the island state of Tasmania, an area classified predominantly as 'regional' by the Australian Standard Geographical Classification - Remoteness Area system^[10]. While there are hepatology specialists available for consultation, there is no dedicated hepatology ICU service or liver transplant center available in Tasmania. The study was approved by the Tasmanian Human Research Ethics Committee (Reference number H0014142).

Patients were followed up to 30 days after discharge from hospital after an ICU admission, using state death registries as well as hospital medical records. Information collected included demographic data; reason for ICU admission; cause and time of death (if relevant); as well as biochemical and/or clinical components (during the first 24 hours of admission) and overall calculated values of the following 3 ICU-specific scores: Sequential Organ Failure Assessment (SOFA)^[11], Simplified Acute Physiology (SAPS II)^[12], Acute Physiology and Chronic Health Evaluation II (APACHE II)^[13]; and the following 2 liver-specific scores: Model for End-Stage Liver Disease (MELD)^[14] and Child-Pugh^[15].

Vital signs recorded included heart rate, blood pressure, temperature, respiratory rate and Glasgow coma scale (GCS). The latter two values were collected prior to mechanical ventilation, where relevant. Other parameters recorded included arterial blood gas parameters, serum sodium, potassium, bicarbonate, urea, creatinine, bilirubin, white cell count (WCC), international normalised ratio (INR), haematocrit, platelet count, weight and urine output. Further information collected included type of admission (emergency surgical, emergency medical or elective), the presence of coexisting chronic cardiovascular, respiratory or renal disease or immunosuppression; and the level, if relevant, of mechanical ventilation or vasopressor use. In regards to cirrhotic status, information was collected about the presence of prior or current esophageal varices (as diagnosed on endoscopy), hepatic encephalopathy (defined as confusion with clinically observed asterix), ascites and spontaneous bacterial peritonitis (SBP, defined as a polymorphonuclear cell count >250 per mm³ in ascitic fluid).

Short-term mortality was defined as death during, or within 30 days of discharge home from, a hospital admission that necessitated

time in ICU. This was to capture patients who died on the hospital wards after discharge from ICU, those who were deemed terminal and moved out of ICU for palliative care, and those who were discharged from hospital only to die within 30 days. Patients were classified accordingly into groups labelled 'survivors' or 'non-survivors' for comparison. Between these groups, Fisher's exact testing with two-tailed p-values was used to compare proportions of categorical variables and two-sampled t testing with equal variances used to compare means of continuous variables. Univariate Cox proportional logistic regression was then used to identify variables associated with short-term mortality (excluding composite severity scores). These were entered into a multivariate, backward, stepwise multiple logistic regression model. Receiver-operating curves for short-term mortality were constructed for the aforementioned severity scores and areas under the receiver-operating curves (AUROC) calculated to determine prognostic accuracy. The Youden Index (sensitivity + specificity - 1)^[16] was used to select the best cut-off point for each score, at which sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were calculated. All statistical analysis was performed with Stata 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and MedCalc Statistical Software version 15.11.4 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2015). *P*-values <0.05 were considered statistically significant.

RESULTS

Eighty-five patients were admitted to the Royal Hobart Hospital ICU between 01/01/2007 and 31/12/2013. 60% male and median age 56 years. Major contributors to cirrhosis were alcohol (68, 60%) and hepatitis C (55, 35%) with 25 (29%) having both contributors. Twelve (15%) had other causes including non-alcoholic fatty liver disease (7), haemochromatosis (2), primary biliary cirrhosis (1), biliary atresia (1) and cardiac cirrhosis (1). Major indications for ICU admission included: variceal bleeding (22, 27%), routine care post elective operation (13, 15%) and infections (excluding SBP) (16, 19%). Infections included pneumonia detected on chest X-ray with no bacterial isolates (6), staphylococcus aureus bacteremia (3), urinary tract infection with mixed enteric flora on urinary cultures (2), streptococcus pneumoniae bacteremia (1), escherichia coli bacteremia (1), listeria monocytogenes meningitis (1), influenza A detected on throat swab nucleic acid testing (1) and cellulitis with no bacterial isolates (1). Details are presented in table 1.

Twenty-four patients (28%) died in the short-term. Causes of death included variceal bleeding (4, 16.7%), hepatorenal syndrome (3, 12.5%), SBP (3, 12.5%), other infections (7, 29%), head trauma (3, 12.5%), progressive encephalopathy (2, 8.3%) and gastrointestinal bleeding of unknown cause (1, 4%). Ten patients (41%) died in ICU (median length of stay 7 days, range 1-19 days). Eleven (46%) died in hospital wards after discharge from ICU (median length of stay on wards 8 days, range 1-16 days). Another 3 (12.5%) died within 30 days of hospital discharge (median length of stay 24 days, range 3-26 days). Clinical and serum laboratory parameters at time of admission are presented in table 2.

Categorical and continuous variables significantly associated with short-term mortality on univariate logistic regression are summarised in table 3.

Notably, the only indication for ICU admission significantly associated with short term mortality was infection excluding SBP, whereas SBP and other cirrhosis-specific indications such as variceal bleeding and encephalopathy were not. Neither were albumin, INR,

age or cause of cirrhosis. Significantly associated variables included need for cardiorespiratory support, renal failure (as measured by serum creatinine), acidosis, decreased GCS and increased WCC. Interestingly there was a negative association between prior or current varices and short-term mortality, though not current variceal bleeding alone. On multivariate multiple logistic regression none of the above parameters independently predicted short-term mortality, likely due to a small sample size.

Non-survivors had significantly higher scores on all scoring systems except Child-Pugh as presented in table 4.

Furthermore the Child-Pugh score had poor correlation with mortality as seen by an area under the Receiver-Operator Curve (AUROC) of 0.57. However MELD, APACHE II, SAPS II and

SOFA scores showed improving correlation with short-term mortality with AUROCs of 0.69, 0.75, 0.79 and 0.81 respectively (Figure 1).

Table 5 presents the optimal cut-off points for each score with associated sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV).

Table 1 Demographic details and reasons for ICU admission.

Variable (unit)	All patients (n = 85)	Survivors (n = 61)	Non-survivors (n = 24)	p value
Age (years)	55.3 ± 12.7	54.9 ± 12.7	56.1 ± 10.2	0.71
Sex (n, %)				
Male	51 (60)	36 (59)	15 (63)	0.81
Female	34 (40)	25 (41)	9 (37)	
Contributors to cirrhosis (n, %)				
Alcohol	68 (60)	48 (79)	20 (83)	0.63
Hepatitis C	55 (35)	19 (31)	11 (46)	0.21
Both alcohol and hepatitis C	25 (29)	15 (25)	10 (42)	0.18
Other	12 (14)	8 (13)	4 (17)	0.73
Child Pugh Score Category (n, %)				
A	9 (11)	7 (11)	2 (8)	0.89
B	29 (34)	21 (34)	8 (33)	
C	47 (55)	33 (54)	14 (58)	
Reason for ICU admission (n, %)				
Variceal bleed	22 (26)	18 (30)	4 (17)	0.28
Encephalopathy	9 (11)	8 (13)	1 (4)	0.28
SBP	3 (4)	2 (3)	1 (4)	1.0
Other medical	9 (11)	7 (11)	2 (8)	1.0
Other infection (excluding SBP)	16 (19)	7 (11)	9 (37)	0.01*
astroduodenal bleed	8 (9)	5 (8)	3 (13)	0.68
Post-operative	13 (15)	11 (17)	2 (8)	0.33
Trauma/emergency surgery	5 (6)	3 (5)	2 (8)	0.61

Age presented as mean ± standard deviation; *= statistically significant.

Table 2 Clinical and serum laboratory variables in the first 24 hours of ICU admission.

Variable (unit)	All patients (n = 85)	Survivors (n = 61)	Non-survivors (n = 24)	p value
Cardiorespiratory support (n, %)				
Need for ionotropes	36 (42)	18 (30)	18 (75)	<0.01*
Need for respiratory support	46 (54)	27 (44)	19 (79)	<0.01*
Presence of cirrhotic complications (n, %)				
Ascites	42 (49)	32 (52)	11 (44)	0.63
Encephalopathy	37 (44)	26 (43)	11 (44)	0.81
Prior or current esophageal varices	50 (59)	40 (66)	10 (42)	0.053
Vital signs				
Lowest systolic blood pressure (mmHg)	102.4 ± 15.3	102.7 ± 14.2	101.5 ± 18.2	0.58
Highest heart rate (beats per minute)	90.0 ± 28.5	90.0 ± 25.3	91.0 ± 35.8	0.83
Highest respiratory rate (respirations per minute)	23.4 ± 7.3	23.0 ± 7.0	24.4 ± 8.0	0.39
Lowest GCS	12.3 ± 3.9	13.0 ± 3.5	10.8 ± 4.4	0.02*
Serum variables				
Sodium (mmol/L)	134.9 ± 5.5	135.2 ± 5.1	134.2 ± 6.6	0.44
Potassium (mmol/L)	4.4 ± 0.8	4.3 ± 0.8	4.5 ± 0.9	0.29
pH	7.34 ± 0.18	7.37 ± 0.15	7.24 ± 0.22	<0.01*
Bicarbonate (mmol/L)	20.4 ± 5.8	21.8 ± 5.3	17.0 ± 5.37	<0.01*
Urea (mmol/L)	11.3 ± 10.2	9.9 ± 10.2	14.7 ± 9.5	0.052
Creatinine (µmol/L)	127.3 ± 101.1	109.2 ± 80.1	173.2 ± 132.4	0.01*
Bilirubin (µmol/L)	82.8 ± 99.6	69.6 ± 69.4	116.2 ± 148.4	0.052
WCC (x10 ⁹ /L)	10.6 ± 7.1	9.5 ± 5.9	13.6 ± 9.1	0.02*
Haematocrit (%)	28.6 ± 7.5	28.6 ± 7.2	28.7 ± 8.6	0.96
Platelet count (x10 ⁹ /L)	123.6 ± 81.3	127.5 ± 90.8	113.7 ± 49.7	0.48
Albumin (g/L)	24.9 ± 6.1	25.0 ± 5.8	24.7 ± 6.8	0.84
INR	1.7 ± 0.7	1.7 ± 0.7	1.9 ± 0.7	0.11

Continuous data presented as mean ± standard deviation; *= statistically significant.

Table 3 Statistically significant variables predicting short-term mortality with univariate logistic regression analysis.

Variable	Odds ratio for short-term mortality (95% CI)	P value
Categorical variables		
Infection (excluding SBP)	4.6 (1.5-14.5)	<0.01
Need for ionotropes	7.2 (2.44-21.0)	<0.01
Need for respiratory support	4.8 (1.6-14.4)	<0.01
Prior or current esophageal varices	0.37 (0.14-0.99)	0.047
Continuous variables		
Increased WCC (per 10 ⁹ /L)	1.08 (1.01-1.16)	0.015
Increased creatinine (per µmol/L)	1.01 (1.0-1.01)	0.020
Decreased pH (per 0.01 units)	1.04 (1.01-1.08)	<0.01
Decreased GCS (per 1 scoring point)	1.15 (1.02-1.29)	0.025

Table 4 Performance of scoring systems predicting short-term mortality.

Scoring system	All patients (n = 85)	Survivors (n = 61)	Non-survivors (n = 24)	P-value
Child-Pugh	9.9 ± 2.4	9.9 ± 2.5	10.0 ± 2.2	0.72
MELD	17.7 ± 9.1	15.8 ± 7.5	22.5 ± 10.9	<0.01
APACHE II	19.2 ± 8.2	17.2 ± 7.4	24.2 ± 8.3	<0.01
SAPS II	44.2 ± 16.0	40.0 ± 14.4	55.0 ± 14.9	<0.01
SOFA	9.2 ± 4.3	7.9 ± 3.5	12.5 ± 4.4	<0.01

All data presented as mean ± standard deviation.

Table 5 Optimal cut-off points for scoring systems.

Scoring system	Cut-off point	Youden Index	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Child-Pugh	7	0.16	91.6	24.6	32.4	88.2
MELD	16.3	0.33	79.1	54.1	40.4	86.8
APACHE II	21	0.49	70.8	78.7	56.7	87.3
SAPS II	45	0.50	75	75.4	54.5	88.5
SOFA	9	0.50	75	75.4	54.5	88.5

DISCUSSION

In our cohort neither presentations specific to cirrhotic patients such as variceal bleeding, encephalopathy and SBP; nor the presence of cirrhotic complications such as ascites or prior/current esophageal varices; were significantly associated with higher short-term mortality after ICU admission. Instead, neurological dysfunction as measured by decreased GCS, cardiorespiratory compromise and sepsis were associated. Acidosis, white cell count rise and renal impairment represent metabolic endpoints of such conditions and as such were also associated with mortality. ICU-specific severity scores taking into account cardiorespiratory dysfunction such as APACHE II, SAPS II and SOFA were thus more accurate in predicting mortality than liver-specific severity scores such as Child-Pugh and MELD which, though widely applicable in many clinical settings, were not designed to assess patients in ICU. MELD likely outperformed Child-Pugh due to its inclusion of creatinine as a measured variable, and indeed acute kidney injury has been extensively shown in international literature to be a poor prognostic indication in hospital-admitted cirrhotics^[17].

The overall in-hospital mortality of 25% (21 of 85 patients) was significantly lower than in previous studies^[18], despite 55% being Child Pugh category C. This may have been a result of a high proportion being admitted for routine post-operative care rather than for unplanned organ dysfunction. Furthermore, selection bias may have applied wherein cirrhotics who were denied ICU admission on the basis of severe illness were not captured in our data, therefore not contributing to mortality rates. An unusual finding was that patients with prior or current esophageal varices were more likely to be survivors than non-survivors on univariate logistic regression. One possible explanation is that many of these patients may have been diagnosed on routine screening, indicating engagement with hepatology services and better management of their cirrhosis prior to ICU admission. Furthermore, bleeding varices as an admission indication to ICU was not associated with greater short-term mortality: the efficacy of endoscopic treatment of bleeding varices has steadily greatly over time^[19] and 6-week rates of survival are approximately 80%^[20]. The high 30-day survival in patients admitted to ICU for variceal bleeding in our study (18 of 22, 81%) is congruent with the broader literature.

Our study is limited by a small sample size which subsequently limited the yield of multivariate analysis. Furthermore, the difficulty of prognosticating patient outcomes within the first 24 hours of ICU admission has been highlighted by other authors^[21] as this may not allow enough time for therapeutic interventions to take maximal effect. Many ICU clinicians may therefore often re-assess prognosis after a 72 hour trial of therapy^[7]. Nevertheless, a strength of our study was following up patients for 30 days post discharge which was felt to be a more clinically appropriate indicator of the success of ICU admission than in-hospital survival, as measured in other studies^[8,22]. It is notable that the vast majority of cirrhotics discharged home from our hospital (61/64, 95%) continued to survive for at least 30 days, which argues strongly against the futility of their ICU admission. Despite being conducted in a regional hospital without specialist transplant services or a dedicated hepatology ICU, our findings reflect those of previous studies in larger centers. Levesque *et al*^[23], in a study of 377 cirrhotics, found that SOFA and SAPS II within the first 24 hours admission had AUROCs for mortality of 0.92 and 0.89, outperforming MELD or Child-Pugh scores with AUROCs of 0.79. Cardiorespiratory support and infection were predictors of mortality on multivariate analysis. Cholongitas *et al*^[24], studying 312 cirrhotics,

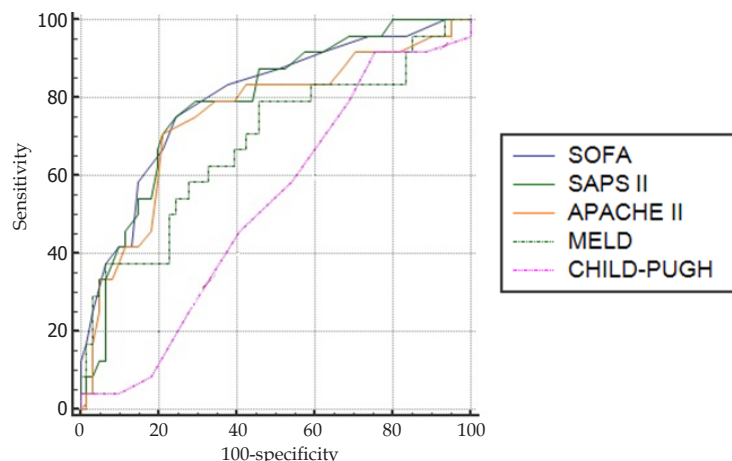


Figure 1 Receiver Operating Characteristic curves for scoring systems.

found that SOFA had an AUROC of 0.83, outperforming MELD and Child-Pugh (AUROC 0.81 and 0.72 respectively). Theochidou *et al*^[8], studying 635 cirrhotics, found SOFA to have an AUROC of 0.81, outperforming MELD and Child-Pugh (AUROC 0.79 and 0.67 respectively), for in-hospital mortality. Indeed in the latter two studies, variceal bleeding was negatively correlated with mortality.

The mortality of cirrhotics admitted to ICU is associated strongly with cardiorespiratory, neurological and metabolic disturbances, as well as infections and renal dysfunction. This is reflected in the improved accuracy of ICU-specific severity scores that encompass such variables, rather than liver-specific scores. Clinicians should take these variables into account when considering the appropriate allocation of ICU resources to cirrhotics, rather than basing assumptions of futility on the level of hepatic dysfunction alone.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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