

Risk factors, Sequential Organ Failure Assessment and Model for End-stage Liver Disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit

E. CHOLONGITAS*, M. SENZOLO*, D. PATCH*, K. KWONG*, V. NIKOLOPOULOU*, G. LEANDRO*, S. SHAW† & A. K. BURROUGHS*

*Liver Transplantation and Hepatobiliary Medicine Unit,
†Department of Intensive Care, Royal Free Hospital, London, UK

Correspondence to:
Professor A. K. Burroughs, Liver Transplantation and Hepatobiliary Medicine Unit, Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG, UK.
E-mail:
andrew.burroughs@royalfree.nhs.uk

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SUMMARY

Background

Prognostic scores in an intensive care unit (ICU) evaluate outcomes, but derive from cohorts containing few cirrhotic patients.

Aims

To evaluate 6-week mortality in cirrhotic patients admitted to an ICU, and to compare general and liver-specific prognostic scores.

Methods

A total of 312 consecutive cirrhotic patients (65% alcoholic; mean age 49.6 years). Multivariable logistic regression to evaluate admission factors associated with survival. Child-Pugh, Model for End-stage Liver Disease (MELD), Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were compared by receiver operating characteristic curves.

Results

Major indication for admission was respiratory failure (35.6%). Median (range) Child-Pugh, APACHE II, MELD and SOFA scores were 11 (5–15), 18 (0–44), 24 (6–40) and 11 (0–21), respectively; 65% ($n = 203$) died. Survival improved over time ($P = 0.005$). Multivariate model factors: more organs failing (FOS) ($<3 = 49.5\%$, $\geq 3 = 90\%$), higher FiO_2 , lactate, urea and bilirubin; resulting in good discrimination [area under receiver operating characteristic curve (AUC) = 0.83], similar to SOFA and MELD ($AUC = 0.83$ and 0.81 , respectively) and superior to APACHE II and Child-Pugh ($AUC = 0.78$ and 0.72 , respectively).

Conclusions

Cirrhotics admitted to ICU with ≥ 3 failing organ systems have 90% mortality. The Royal Free model discriminated well and contained key variables of organ function. SOFA and MELD were better predictors than APACHE II or Child-Pugh scores.

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INTRODUCTION

Decompensated cirrhosis has a poor prognosis with a 6-year survival of only 21%.¹ The mortality rate is much higher when cirrhotic patients require admission to intensive care unit (ICU).²⁻⁴ Thus, the decision to initiate intensive care is frequently questioned as cirrhotic patients often progress to multi-organ failure.^{4, 5}

Currently, liver transplantation (LT) is the only curative therapy for established cirrhosis, giving excellent long-term survival. However, because of increasing waiting times for transplantation, some patients will deteriorate, precipitating ICU admission,⁶ and in addition non-transplant candidates may still need ICU care. These admissions are costly, and in many countries (including the UK) there is limited ICU bed availability. Thus, being able to identify those cirrhotic patients who may benefit most from continued ICU care would be very useful. To help in this, the clinical and laboratory variables that are associated predictively with mortality, need evaluation to see if objective scoring systems, providing accurate estimates for predicting outcomes, can be derived.⁷

The Child and Turcotte classification (1964) and the Pugh's modification (1973) have been widely used for the assessment of the severity of liver disease.^{8, 9} These liver-specific prognostic scores for stratifying cirrhotic patients into risk groups for surgical treatment, sclerotherapy or transjugular intrahepatic portosystemic shunt (TIPS) are useful.¹⁰⁻¹³ However, the Child-Pugh (CP) scoring system has some subjective components and does not score other factors such as cardiovascular, renal and pulmonary dysfunction,^{2, 7, 14} which are relevant in an intensive care setting.

The Model for End-stage Liver Disease (MELD) score is a new liver-specific prognostic model, currently used in donor liver allocation systems in the USA. It has been validated for 3-month survival in cirrhotics,^{15, 16} but its accuracy has never been evaluated in cirrhotic patients admitted to ICU.

The Acute Physiology And Chronic Health Evaluation (APACHE) II¹⁷ and the Sequential Organ Failure Assessment (SOFA)¹⁸ (Figure 1) are ICU-specific prognostic scores, developed from general ICU populations and widely used. The predictive accuracy of these two scores in critically ill cirrhotic patients has been evaluated in only a few studies^{6, 7, 19-24} and only two, both from the same centre, had a cohort of over 200 cirrhotics.^{22, 23} Indeed, there are data from only 10

Variables/score	0	1	2	3	4
Respiratory ($\text{PaO}_2/\text{FiO}_2$, mmHg)	>400	≤400	≤300	≤200	≤100
Coagulation ($\text{PLT} \times 10^3/\mu\text{L}$)	>150	≤150	≤100	≤50	≤20
Liver (Bilirubin, mg/dL)	<1.2	1.2–1.9	2–5.9	6–11.9	>12
Cardiovascular ($\mu\text{g}/\text{kg}/\text{min}$)	-	MAP < 70	Dop ≤ 5	Dop > 5 (Epi ≤ 0.1)	Epi > 0.1
CNS (GCS)	15	13–14	10–12	6–9	<6
Renal (Creatinine, mg/dL)	<1.2	1.2–1.9	2–3.4	3.5–4.9	>5

MAP: mean arterial pressure, Dop: dopamine, Epi: epinephrine
GCS: Glasgow coma scale

Figure 1. Appendix: calculation of failing organ systems using three points or more in the Sequential Organ Failure Assessment (SOFA) score.

centres published in 15 articles concerning prognostic scores in cirrhotic patients admitted to ICU during the last 20 years.^{2, 6, 7, 19-30}

Our aim was firstly to evaluate short-term mortality in a large cohort of cirrhotic patients considering clinical variables on the day of admission to ICU, to identify the predictive factors for mortality and to derive our (Royal Free Hospital) score. Secondly, to compare the prognostic survival model, with liver-specific scores CP, MELD, and to ICU scores, APACHE II and SOFA. Thirdly, to examine whether mortality was changing over time.

PATIENTS AND METHODS

Consecutive cirrhotic patients with their first admission to the ICU, Royal Free Hospital (RFH), between 1 January 1989 and 31 August 2004 were evaluated. The diagnosis of cirrhosis was confirmed by the combination of at least two of three parameters: presence of varices, imaging or liver biopsy. All patients were followed up to 6 weeks after discharge from ICU or less if death had occurred earlier. We excluded patients who either underwent liver transplant before admission, during their stay in ICU or within 6 weeks after discharge from ICU. Non-survivors were defined as those who died either in ICU or within 6 weeks after discharge from the ICU. The period of 6 weeks was chosen so as to include those who died on the general wards following their discharge from ICU, who are often not included in ICU statistics and to encom-

pass those patients in whom a decision had been made not to resuscitate further, and thus returned to the wards for terminal care.

The following demographic and clinical variables were prospectively recorded for each patient on admission to ICU: age, sex, transfer from RFH general ward or other hospital and length of stay in general ward (RFH or other hospital) before ICU admission. On admission to the ICU, white blood count (WBC), platelet count (PLT), creatinine (Cr), urea (Ur), sodium (Na), potassium (K), inspiratory concentration of oxygen (FiO_2), arterial blood gas [pH, partial arterial pressure of oxygen (PaO_2) and carbon dioxide (PaCO_2)] and acid base, lactate, albumin, bilirubin (BIL) and clotting profile [prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT)] were recorded.

With regard to mode of presentation to the hospital and the indication for transfer from the general ward to the ICU, these were defined as: (i) liver failure, i.e. hepatic encephalopathy >2 grade and/or $\text{PT} > 50$ s, and/or $\text{BIL} > 300 \mu\text{mol/L}$; (ii) cardiac or respiratory failure if there was use of inotropes and/or cardiac arrest or mechanical ventilation respectively. Patients requiring ventilation electively for airway protection in order to use balloon tamponade were not considered to have respiratory failure; (iii) renal failure as $\text{Cr} \geq 300 \mu\text{mol/L}$, presence of hepatorenal syndrome or need for haemofiltration; (iv) multiple organ failure if there was combined cardiac, respiratory and renal failure; and (v) presence of sepsis, as proposed by the ACCP/SCCM consensus conference.³⁰ If the patient was already paralysed or sedated, the patient was not considered in neurological failure.

During the ICU stay, gastrointestinal (GI) bleeding episodes, development of aspiration pneumonia and additional use of inotropes, mechanical ventilation or haemofiltration were also recorded. Severity of liver disease was evaluated by the CP and MELD scores. APACHE II was used for classification of illness severity and the SOFA score for grading of organ dysfunction or failing organ systems (FOS). The presence of FOS on ICU admission was defined as a SOFA score of 3 or more points for any individual organ. All the above scoring systems were calculated as published and were evaluated on the first day of the ICU admission.^{16–18} Finally, the length of stay in the ICU as well as in the general ward after discharge from ICU was also recorded.

Statistical methods

Univariate comparisons of demographic and baseline clinical factors between patients who died in ICU or within 6 weeks after discharge and those who remained alive for more than 6 weeks after discharge were performed using Mann–Whitney *U*-tests for continuous variables and chi-square tests for categorical variables. To identify ICU-admission factors that were independently associated with mortality, multivariable logistic regression analysis was performed and a prognostic score was calculated. The discrimination ability of all published models to predict the outcome of cirrhotic patients (either dead or alive) was evaluated by using the area under a receiver operating characteristic (ROC) curve. This has the true-positive and false-positive rates on the vertical and horizontal axes respectively. In this analysis, a model with an area under the ROC curve (*AUC*) between 0.7 and 0.8 is considered clinically useful and between 0.8 and 0.9 as having excellent diagnostic accuracy. As the *AUC* approaches 1.0, the model approaches 100% sensitivity and specificity.³¹ To test the calibration (i.e. the degree of correspondence between predicted and observed mortality) we used goodness-of-fit testing to evaluate the calibration using the Hosmer–Lemeshow test. A high *P*-value in this test (close to 1.0) is considered good calibration.³² The Youden Index (sensitivity + specificity – 1)³³ was used to select the best cut-off point, at which sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were calculated and at which the patients could be correctly classified for each prognostic model. A *P*-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 312 cirrhotic patients were admitted during the study period: 182 (58.3%) were male and the mean age was 49.3 ± 11 years (Table 1). Alcohol was the cause of cirrhosis in 203 (65%) patients. The remaining causes are shown in Table 2. Two hundred and eight (67%) cirrhotic patients were transferred from RFH general wards and the remaining 33% directly to ICU from other hospitals. The median number of days in the general ward before ICU admission was two (range 1–120) (Table 1). The initial presentation to the hospital was GI bleeding in 55.5%, sepsis in 9%, hepatic failure 6.5%, respiratory failure 6.4%, renal failure 8%

Table 1. Clinical and laboratory characteristics of cirrhotic patients on admission to intensive care unit (ICU)

Variable (unit)	All (n = 312)	Survivors (n = 109, 34.9%)	Non-survivors (n = 203, 65.1%)	P
Age (years)	49 ± 11	48 ± 12	53 ± 11	0.84
Sex, n (%)				
Male	182	65 (60)	117 (58)	0.73
Female	130	44 (40)	86 (42)	
Admission year, n (%)				
1989–1996	151	41 (38)	110 (54)	0.006
1997–2004	161	68 (62)	93 (46)	
Transfer from RFH	208	55	153	<0.001
Days in the ICU	4 (1–48)	4 (1–48)	4 (1–36)	0.07
Days in the ward	2 (0–120)	2 (0–34)	2 (0–120)	0.67
Cardiac arrest, n (%)	24	1(1)	23 (11)	<0.001
On admission to ICU, n (%)				
Antibiotics used	293	104 (95)	189 (93)	0.13
Gastrointestinal bleeding	191	81 (74)	110 (54)	0.001
Inotropic support	193	50 (46)	143 (70)	<0.001
Mechanical ventilation	275	94 (86)	181 (89)	0.46
Encephalopathy (grade 3,4)	109	24 (22)	85 (42)	0.001
Ascites (yes)	270	88 (81)	182 (90)	0.04
During ICU stay, n (%)				
Gastrointestinal bleeding	62	13 (12)	49 (24)	0.004
Mechanical ventilation	277	91 (83)	186 (92)	0.03
Inotropic support	254	71 (65)	183 (90)	<0.001
Renal failure	127	11 (10)	116 (57)	<0.001
Haemofiltration	56	5 (5)	51 (25)	<0.001
Albumin (g/L)	28.7 ± 8.3	28 ± 7.7	29 ± 8.7	0.39
WBC (10 ⁹ /L)	10.8 (0.8–52)	8.2 (0.8–35)	11 (1.3–52)	0.002
PLT (10 ⁹ /L)	70 (8–1166)	77 (11–586)	67 (8–1166)	0.09
Bilirubin (μmol/L)	87 (2–922)	52 (9–529)	124 (2–922)	<0.001
Prothrombin time (s)	25 (13–124)	22 (13–48)	28 (14–124)	<0.001
Creatinine (μmol/L)	102 (21–995)	78 (48–995)	124 (21–924)	<0.001
Urea (mmol/L)	10.2 (0.8–52)	7.7 (2–45)	14 (0.8–52)	<0.001
Na (mmol/L)	137 ± 10	138 ± 7.7	136 ± 11	0.047
K (mmol/L)	4.2 ± 0.9	4 ± 0.8	4.2 ± 1	0.15
Lactate (mmol/L)	2.3 (0.1–21)	1.5 (0.1–11.8)	3.1 (0.1–21)	<0.001
FiO ₂ (%)	0.58 ± 0.2	0.5 ± 0.1	0.6 ± 0.2	<0.001
pH	7.3 ± 0.1	7.41 ± 0.1	7.3 ± 0.1	<0.001
Number of FOS (%)				
<3	69	92	55	<0.001
≥3	31	8	45	

FOS, failing organ system; RFH, Royal Free Hospital; PLT, platelet count; WBC, white blood count.

and others 14.6%. Of the 172 patients with GI bleeding on admission to the hospital, 115 (66.8%) already had complications such as aspiration pneumonia, severe infection or organ failure. Twenty-four cirrhotic patients had suffered from cardiac arrest before ICU admission (Table 1). In the cohort of 312, seven had already been placed on a LT waiting list. Their characteristics were not significantly different from those who were not on a waiting list at the time of admis-

sion to ICU. No patient underwent LT within 6 weeks of ICU discharge, but 13 did so between 20 and 96 weeks.

In terms of indications for admission to the ICU, 35.6% had respiratory failure, 22% GI bleeding, 7.1% liver failure, 12.5% renal failure, 6.4% cardiac failure, 5.8% sepsis, 2.2% multiple organ failure and 8.4% other causes (Table 2); 191 cirrhotic patients had GI bleeding on admission to ICU (Table 1). Most bled

Table 2. Aetiology of liver cirrhosis and indication for intensive care unit (ICU) admission in Royal Free Hospital cohort of patients treated in the intensive care unit

	All patients (n = 312)	Survivors (n = 109)	Non-survivors (n = 203)
Cause of cirrhosis*			
Alcohol	203	75	128
Non-alcoholic	109	34	75
Viral (hepatitis B or C)	54	15	39
Autoimmune	13	3	10
Cryptogenic	14	6	8
Primary biliary cirrhosis	10	5	5
Others†	18	5	13
Indication for ICU admission**			
Gastrointestinal bleeding	69	42	27
Other indications			
Respiratory failure	111	37	74
Liver failure	22	6	16
Sepsis	18	3	15
Renal failure	39	3	36
Cardiac failure	20	4	16
Multiple organ failure	7	–	7
Others	26	14	12

* $P = 0.31$, ** $P < 0.001$.

† Other causes included: Wilson disease, primary sclerosing cholangitis, cystic fibrosis, haemochromatosis, congenital and methotrexate induced (three patients died before the cause of liver cirrhosis was known).

from oesophageal varices ($n = 176$), 10 from oesophageal or duodenal ulcers and five from unidentified sites. Emergency TIPS placement was performed in 64 (20.5%) patients. Only four (1.3%) of 312 patients, were CP class A on ICU admission, 66 (21.2%) were class B and the remaining 242 (77.5%) were class C. The median CP, APACHE II, MELD and SOFA scores on admission to ICU were 11 (5–15), 18 (0–44), 24 (6–40) and 11 (0–21) respectively.

On the first day of admission or during hospitalization, 38.8% of the patients had or developed aspiration pneumonia. Mechanical ventilation and cardiovascular support with inotropes were used in the vast majority (88.8% and 81.4% respectively) (Table 1).

Mortality

The overall mortality in ICU or 6 weeks after discharge from ICU was 65.1% (Table 1). Causes of death were: multiple organ failure in 45.6%, respiratory failure in 18.5%, renal failure in 11.8%, uncontrolled variceal bleeding in 8.7%, liver failure in 6.2% and others in 9.2%. The median length of stay in ICU was not different between survivors [4 (1–48) days] and non-survi-

vors [4 (1–36) days, $P = 0.07$] (Table 1). Cirrhotics who died were more likely to be admitted during the period 1989–1996 compared to 1997–2004 (73% vs. 58%, $P = 0.006$) (Table 1). Furthermore, we defined four time periods: 1989–1992 ($n = 46$), 1993–1996 ($n = 105$), 1997–2000 ($n = 91$) and 2001–2004 ($n = 70$), during which there was a progressive and significant decrease in mortality over the years, as shown in Figure 2, with 82% mortality for the first period (1989–1992) compared to 52% for the last period (2001–2004).

Factors associated with mortality in ICU or within 6 weeks after discharge from ICU: univariate analysis

Cirrhotics who died were less likely to have GI bleeding as indication for admission to ICU compared to survivors ($P < 0.001$) (Tables 1 and 2) and more frequently had severe encephalopathy ($P = 0.001$), ascites ($P < 0.001$) and need for cardiovascular support with inotropes ($P < 0.001$). The cohort who died also had significantly higher median values of CP (12 vs. 10), APACHE II (21 vs. 15), MELD (27 vs. 19) and SOFA (12 vs. 9) scores ($P < 0.001$). During the ICU stay,

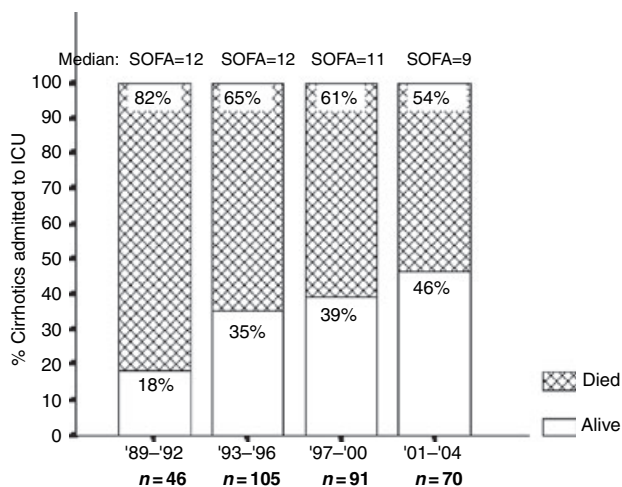


Figure 2. Mortality in a consecutive cohort of cirrhotic patients ($n = 312$) admitted to intensive care unit according to year of admission ($P = 0.005$).

those who died needed ventilatory ($P = 0.03$), cardiovascular ($P < 0.001$) and haemofiltration ($P < 0.001$) support more frequently. However, the use of antibiotics and mechanical ventilation on admission to the ICU and the development of aspiration pneumonia during the ICU stay were not associated with worse survival.

Eleven of the 17 laboratory variables had prognostic value in the univariate analysis: WBC, Cr, Ur, Na, pH, FiO_2 , lactate, BIL, PT, INR and aPTT (Table 1). When there were ≥ 3 FOS on admission, mortality was 90%; if FOS < 3 then mortality was 49% ($P < 0.001$). There was a progressive increase in mortality associated with the number of FOS: cirrhotics with none, one, two or more than three FOS on admission to the ICU had 4%, 45%, 65% and 90% mortality respectively ($P < 0.001$) (Figure 3).

Factors associated with mortality: multivariate logistic regression analysis

Five variables were independently associated with mortality: more FOS, and higher FiO_2 , serum lactate, urea and bilirubin on admission (Table 3). Based on the regression coefficients of these five independent variables, a new prognostic model (RFH scoring system) of mortality was derived with the following mathematical formula:

$$\text{RFH score} = -6.611 + \text{bilirubin}(0.004) + \text{urea}(0.057) + \text{lactate}(0.274) + \text{FiO}_2(3.126) + K$$

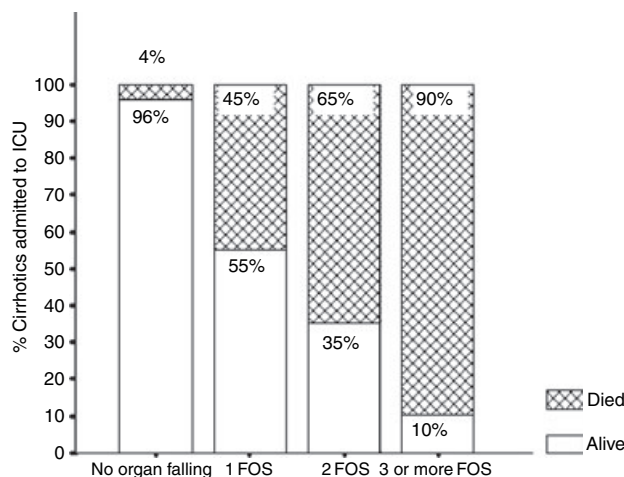


Figure 3. Mortality and number of failing organ systems (FOS) in a consecutive cohort of 312 cirrhotic patients admitted to intensive care unit ($P < 0.001$).

Table 3. Independent risk factors of mortality in Royal Free Hospital centre (multivariate logistic regression analysis)

	OR	95% CI
FiO_2 (per 10%)	22.78	1.97-264
Lactate (per mmol/L)	1.32	1.11-1.56
Urea (per mmol/L)	1.06	1.01-1.11
Bilirubin (per $\mu\text{mol/L}$)	1.04	1.01-1.08
Failing organ system (FOS)		
1	17.6	1.89-165
2	38.2	4.09-356.8
≥ 3	99.1	9.25-1061

$K = 2.872$ if FOS = 1, 3.643 if FOS = 2 and 4.596 if FOS ≥ 3 .

The estimated probability of mortality within 6 weeks of discharge of ICU is: $e^{\text{score}} / (1 + e^{\text{score}})$.

Prognostic factors associated with mortality - receiver-operating characteristic curves

Based on the area under the ROC curves, the SOFA had the best (0.83) discriminative accuracy for mortality ($AUC = 0.83$), followed by the MELD score ($AUC = 0.81$). The APACHE II score had an acceptable discrimination ($AUC = 0.78$) and the CP score had the worst but still acceptable discrimination value ($AUC = 0.72$) (Figure 4). As might be expected, the RFH prognostic

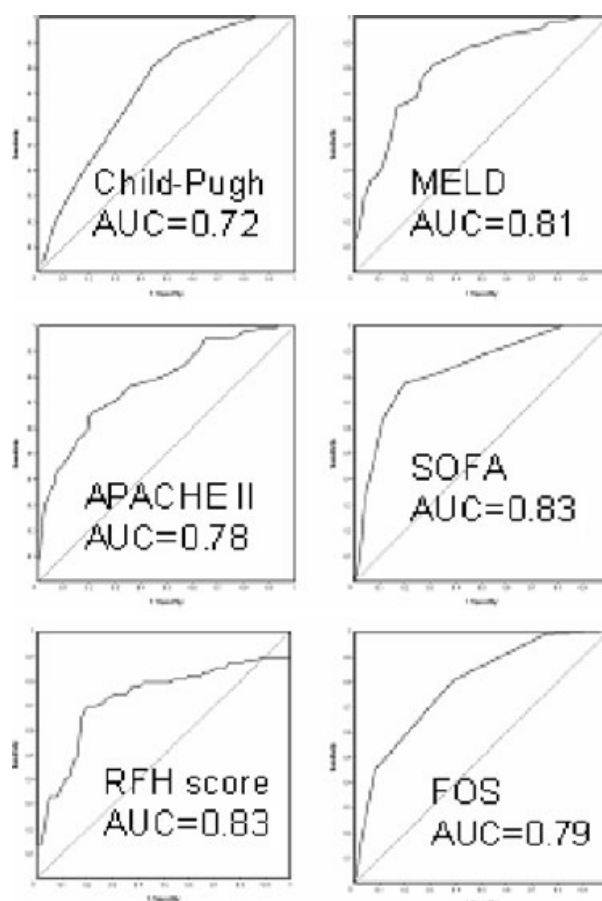


Figure 4. Receiver operating characteristic (ROC) curves for Child-Pugh, Model for End-stage Liver Disease (MELD), Acute Physiology And Chronic Health Evaluation (APACHE II), Sequential Organ Failure Assessment (SOFA), Royal Free Hospital (RFH) intensive care score and failing organ systems (FOS) in 312 consecutive cirrhotic patients admitted to intensive care unit.

score had very good discrimination in our cohort (0.83), similar to the SOFA and MELD scores (Figure 4). From a practical perspective, the number of FOS also had very good discrimination ability ($AUC = 0.79$). Regarding the goodness-of-fit measured by the Lemeshow-Hosmer, the calibration of MELD ($\chi^2 = 3.7$, $P = 0.61$) was superior to SOFA ($\chi^2 = 8.1$, $P = 0.43$) and FOS ($\chi^2 = 3.5$, $P = 0.3$). Table 4 shows the goodness-of-fit, sensitivity, specificity, PPV, NPV and diagnostic accuracy, at the cut-off point giving the best Youden Index for each scoring system. SOFA and MELD scores, following by the RFH score, had the best Youden Index and diagnostic accuracy.

DISCUSSION

Accurate prognostic indicators for patient survival in ICU are important, and help guide clinical decision making, talking to families of patients, as well as allowing comparison to be made between units. This is particularly relevant in cirrhotic patients, as mortality remains high despite intensive support. In our study, we evaluated predictors from patients' clinical and laboratory variables available on ICU admission, to generate a useful prognostic model for cirrhotic patients who require intensive care, and compared its prognostic ability to established scoring systems, both liver-specific (CP and MELD) and ICU scores (APACHE II and SOFA).

Our cohort is the second largest of cirrhotic patients in ICU. The other two cohorts, from the same centre, had included 420 cirrhotic patients.^{22, 23} For the first time we evaluated four established prognostic scores: APACHE II and SOFA (ICU specific) and CP and MELD (liver specific). SOFA had better predictive value

Table 4. Prediction of mortality in 312 cirrhotic patients admitted to intensive care unit

Prognostic score	Cut-off point	Youden Index	Goodness-of-fit (P -value)	Sensitivity (%)	Specificity (%)	PPV	NPV	Diagnostic accuracy
Child-Pugh	11	0.36	0.42	80	56	0.76	0.62	0.71
MELD	22	0.50	0.61	81	69	0.83	0.66	0.77
SOFA	11	0.58	0.43	77	80	0.86	0.69	0.78
APACHE II	19	0.45	0.42	65	80	0.86	0.56	0.70
RFH score	3.2	0.50	0.48	69	81	0.85	0.66	0.72

PPV, positive predictive value; NPV, negative predictive value; RFH, Royal Free Hospital; MELD, Model for End-stage Liver Disease; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology And Chronic Health Evaluation.

($AUC = 0.83$), compared to APACHE II and CP scores ($AUC = 0.78$ and 0.72 respectively). These findings agree with the four most recent series,^{19, 20, 26, 28} in which in all but one,²⁰ showed that ICU-specific scores (APACHE II and/or SOFA) were superior to CP, and SOFA always performed better than APACHE II. This is despite the development and validation of SOFA score in general ICU population with heterogeneous reasons for admission with various disease aetiologies, but which included very few cirrhotic patients. In our study, exclusion of PLT count (which are usually low in cirrhotic patients) from SOFA and FOS scores calculation did not increase their performance.

Our study assessed for the first time MELD scores in cirrhotic patients admitted to ICU;^{15, 34} MELD had high discrimination ($AUC = 0.81$) almost the same as SOFA and superior to APACHE II. Moreover, MELD had better calibration than the other prognostic scores.

The comparable performance of MELD and SOFA scores is partly explained by both having bilirubin and creatinine as components. In addition, both scores have surrogate variables related to more than one organ dysfunction. In SOFA, low platelet counts reflect advanced cirrhosis and not only haematological dysfunction. High MELD scores can be associated with extra-hepatic causes such as severe sepsis (increased bilirubin and prolonged INR), haemolysis (high bilirubin) and intrinsic renal or cardiac failure (raised serum creatinine).

In our large cohort we derived a specific prognostic score for cirrhotic patients admitted to ICU. It had very good efficiency ($AUC = 0.83$) similar to SOFA and MELD scores but needs validation in other cohorts. This is particularly important as the mortality was decreasing with time, despite similar characteristics at admission to ICU. Although the possible reasons reside in better therapies and management for bleeding, renal failure and sepsis, which may not affect the scoring variables, this requires specific testing in new cohorts. The prognostic factors in our model were all associated with organ dysfunction, both quantitatively (number of FOS) and qualitatively: FiO_2 , bilirubin, urea and lactate. This emphasizes that liver-specific scores on their own may not be useful in the ICU setting and confirms that respiratory insufficiency is an independent factor associated with mortality.^{2, 14, 35} Serum urea, a surrogate marker of renal failure and protein catabolism, was also associated with short-term mortality. The development of renal failure in cirrhotic patients indicates a catastrophic reduction in survival probability, such that it is the predominant

factor in end-stage cirrhosis.^{28, 36–38} The CP score does not contain variables of renal function, and this may be why it had the worst performance.

Although the precise mechanisms of hyperlactaemia in severe liver dysfunction are not elucidated precisely,³⁹ serum lactate predicts mortality in paracetamol-induced acute liver failure⁴⁰ and is used to assess severity of acute liver failure in general.⁴¹ However, surprisingly, there is only one other study in critically ill cirrhotic patients, which evaluated lactate, which also found that it was independently associated with mortality.²¹

The current published scoring systems are complicated, requiring hand-held computers or pocket charts for calculation, and as a result have not become completely incorporated into daily clinical practice, but are used retrospectively for audit and quality control purposes.⁴² In our study, the SOFA and MELD scores had better predictive ability, compared to APACHE II, but they are not without drawbacks. In the SOFA, similar to APACHE II, accurate neurological assessment is difficult in intubated patients and its development was based on very few patients with cirrhosis. The MELD score also requires computer calculation and it does not provide clinical information on organ dysfunction, so its accuracy for cirrhotic patients admitted to ICU needs further validation. Although the CP score had the lowest efficiency ($AUC = 0.72$) and incorporates subjective variables, it is simpler than the other three scores. It remains a convenient scoring system with acceptable discriminative power and could be improved by the addition of creatinine.^{43, 44}

An alternative approach for predicting mortality could be the number of FOS assessment. In our study, the main cause of death was multiple organ failure and the mortality rate in patients without any FOS was only 4% compared to 90% of those with three or more FOS (Figure 3). These findings are in accordance with previous studies^{19, 26, 28} and reflect the importance of the number of failing organs in the outcome of cirrhotic patients admitted to the ICU. Our definitions of organ failure, similar to Wehler *et al.*¹⁹ were based on the SOFA score; they do reflect severe organ dysfunction and are easily reproducible. The number of FOS was independently associated with survival and had very good predictive accuracy in terms of the area under the ROC curve ($AUC = 0.79$) (Figure 4). We would argue that this more pragmatic approach uses data that is readily available and does not involve complicated calculation.

Interestingly, there was a significant improvement in survival over the years in our centre (Figure 3). This improvement is not due to selection bias in terms of which patients were evaluated, as all cirrhotic patients who admitted to ICU during the study period were included. During the first three time periods (1989–1992, 1993–1996 and 1997–2000), the improved survival occurred despite the same median SOFA score on admission to ICU. Thus, the improvement in mortality probably reflects: (i) specific improvement in pharmacological (terlipressin, antibiotics) and invasive therapies (endoscopy, TIPS)^{45, 46}; and (ii) better use of haemofiltration and general ICU measures. In the last cohort (2001–2004), survival was even better, but median SOFA score was lower, compared to the previous three cohorts. In our centre, we believe this reflects the earlier admission to ICU, associated with establishment of an outreach team in February 2001.⁴⁷

Our overall mortality was slightly higher than in other recent published series.^{6, 19, 20, 22} However, we included patients who died within 6 weeks after ICU discharge in the non-survivor group. Indeed, 21 (10%) of the 203 deaths occurred after discharge (median 8 days, range 1–35). Although a small group, 23 (96%) of 24 patients with cardiac arrest before ICU admission died, so this group in this setting may not warrant ICU admission or continuing ICU care. One limitation of our study is that it is based on a specialized single referral centre, with patients referred for specific therapy, particularly for bleeding (therapeutic endoscopy, TIPS). However, our cohort had comparable severity of liver disease, a comparable proportion admitted with GI bleeding to other studies,^{19, 20, 23} and comparable proportion of alcoholic cirrhotic patients.^{20, 22, 23} The second potential limitation is the exclusion of cirrhotic patients who underwent LT during ICU stay or within 6 weeks of discharge from ICU. This criterion was also used by previously published studies. However, all the 13 patients who underwent

transplantation having survived ICU did so after 6 weeks from their discharge and thus do not confound our analysis. This proportion of patients may seem particularly small, and might not be similar in other cohorts, but is explained by the fact that the vast majority of our ICU cohort received mechanical ventilation (88%) and/or inotrope support (81.4%). Most liver transplant centres, including ours, will wait for full recovery of respiratory and circulatory function before transplantation. Those with renal failure who need haemofiltration or dialysis, and survive are required to wait to observe if either recovery takes place, or alternatively a decision is taken for a double liver and kidney transplantation. In practice, this period extends to 6–8 weeks, i.e. beyond the interval over which we assessed survival in this cohort. This approach is also used for those already listed, which were only seven in our cohort. Another factor is the need in alcoholic cirrhotic patients (65% in our cohort) to assess the risk of continued or repeated alcohol abuse, which can only be made when the patient has survived ICU and is stable and the need to have an interval to observe how much improvement in hepatic function there may be. Both these factors delay a decision to list for LT by several weeks.

In conclusion, in cirrhotic patients requiring ICU admission or undergoing treatment in ICU, appropriate weighting can be allocated to the number of organ failures, to aid a decision to admit to an ICU bed or to withdraw therapy once in ICU. Although this approach should be prospectively validated, currently many centres do not admit cirrhotic patients to ICU, who have three or more organ system failures, particularly when renal failure is present.

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