Increased Survival for Patients With Cirrhosis and Organ Failure in Liver Intensive Care and Validation of the Chronic Liver Failure–Sequential Organ Failure Scoring System

Mark J. W. McPhail,[*,‡] Debbie L. Shawcross,[*] Robin D. Abeles,[*] Anthony Chang,[*] Vishal Patel,[*] Guan-Huei Lee,[*] Maheeba Abdulla,[*] Elizabeth Sizer,[*] Christopher Willars,[*] Georg Auzinger,[*] William Bernal,[*] and Julia A. Wendon[*]

*Institute of Liver Studies, Kings College Hospital, London, United Kingdom; ‡Department of Hepatology and Gastroenterology, St Mary's Hospital Campus, Imperial College, London, United Kingdom

BACKGROUND & AIMS: During the past decade, survival has increased among patients admitted to general intensive care units, but it is not clear if it has increased for patients admitted with cirrhosis and organ failure. The chronic liver failure–sequential organ failure assessment (CLIF-SOFA) recently was developed as an adaptation to the SOFA to predict outcomes of patients, but requires validation. We investigated changes in outcomes of patients with cirrhosis and organ failure since 2000, compared the abilities of SOFA and CLIF-SOFA to predict patient survival, and validated the CLIF-SOFA system.

METHODS: In a retrospective study, we collected data from 971 patients (median age, 52 y; age range, 16–90 y; 62% male) with cirrhosis (54% alcohol associated, 12% viral, and 34% other causes). The patients were admitted under emergency conditions from January 1, 2000, to December 31, 2010, to a liver intensive therapy unit in the United Kingdom. Patient survival while in the hospital was compared with measures of illness severity, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, model for end-stage liver disease (MELD) scores, SOFA scores, and CLIF-SOFA scores.

RESULTS: Patients had a median APACHE II score of 21 (range, 5–50) and a median MELD score of 23 (range, 6–40). The median APACHE II score at admission decreased from 23 to 22 over the study period ($P < .001$), whereas the median MELD score at admission decreased from 23 to 18 ($P < .001$). Overall survival until hospital discharge was 51%; this value increased from 40% in 2000 to 63% in 2010 ($P < .001$). The unadjusted odds ratio for change in mortality/year was 0.87 (95% confidence interval, 0.83–0.91; $P < .001$). The APACHE II score adjusted odds ratio for mortality was 0.89 (95% confidence interval, 0.84–0.93; $P < .001$). The etiology of cirrhosis was not associated with a significant difference in survival. CLIF-SOFA and SOFA scores at the time of admission predicted patient survival with area under the receiver operating curve (AUROC) values of 0.813 and 0.799, respectively; the scores at 48 hours after admission predicted survival with AUROC values of 0.853 and 0.840, and scores after 1 week predicted survival with AUROC values of 0.842 and 0.844, respectively. These AUROC values were higher than those obtained from APACHE II or MELD scores.

CONCLUSIONS: The proportion of patients with cirrhosis who survived after admission to intensive care increased from 2000 to 2010. SOFA and CLIF-SOFA scores during the first week of critical care appear to have similar abilities to predict patient survival.

Keywords: ICU; Chronic Liver Disease; Prognostic Factor; Prognosis.

Abbreviations used in this paper: ACLF, acute-on-chronic liver failure; APACHE, Acute Physiology and Chronic Health Evaluation; AUROC, area under the receiver operating curve; CLD, chronic liver disease; CLIF, chronic liver failure; GI, gastrointestinal; ICU, intensive care unit; INR, international normalized ratio; LITU, liver intensive therapy unit; OF, organ failure; OR, odds ratio; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.08.041

See editorial on page 1361.

Worldwide, the incidence of chronic liver disease (CLD) is increasing, with expected increases in hospital admissions and liver-related mortality.[1,2] Prognostication is vital in this population because resource use in critical care will be significant[3,4] and evidence-based decisions on the likely outcome might assist in decision making in relation to the delivery of critical care to patient groups most likely to benefit.

Studies reporting survival of critically ill patients with cirrhosis in the intensive care unit (ICU) suggest that overall mortality ranges between 40% and 80%, with a progressive increase in mortality dependent on the number of organ systems failing.[5–8] Although outcomes for the critically ill have improved markedly in recent decades, whether this is also the case for patients with CLD is less well defined.

Survival prediction in patients with CLD originated with the Child–Pugh–Turcotte[9] score and, more recently, the Mayo End-Stage Liver Disease (MELD)[10,11] score, which is now a standard descriptive and prognostic score in patients with cirrhosis.[12]

In patients who require support of one or more extrahepatic organs, intensive care organ failure scoring systems often are used in preference to MELD. The Acute Physiology and Chronic Health Evaluation (APACHE) score has undergone several modifications since its inception[13] and its complex nature means it is seldom used at the bedside to inform treatment decisions, but it is a validated benchmark for ICU mortality rates, in common with the Simplified Acute Physiology Score (SAPS-II).[14]

The sequential organ failure assessment (SOFA)[15] score was developed from expert opinion and produces a simpler score for use beyond the first ICU day and often with increased prognostic accuracy.[5] The SOFA score provides a systems score, an overall score, and also a specific organ failure score, the latter being defined as a score of 3 or 4 for the various organ systems. One potential barrier to the use of these scores is that to predict futility, the statistical power of any score arguably should be higher (and the false-positive rate should be lower) than that of a scoring system used to determine the application of a life-saving therapy such as emergency liver transplantation. At present, none are used to define futility of starting or continuing organ support. Recent reports have suggested that patients with liver disease can be denied admission to intensive care units on the basis of perceived futility.[16] In critically ill patients with cirrhosis, SOFA has been shown to be better than APACHE II or other ICU systems in predicting intensive care unit survival. Furthermore, although SOFA and/or MELD at 48 hours after admission may lead to higher predictive accuracy,[17] this has not been validated or tested further later in admission.

Recently, a chronic liver failure–specific modification of the SOFA score (CLIF-SOFA) from a cohort of patients without multi-organ liver failure and is postulated to have a still higher accuracy for patients with cirrhosis.[18] The CLIF-SOFA accommodates the international normalized ratio (INR) instead of platelets as a coagulation score, increases the threshold for bilirubin to achieve organ failure (OF), and uses grades of hepatic encephalopathy as opposed to Glasgow Coma Scale for neurologic failure.

In this study, we examined a large population of patients with CLD requiring emergent admission and organ support in a critical care environment. Our aim was to describe the changes in outcome over an extended period in a unit that specializes in the care of critically ill patients with liver disease. In a very large longitudinal data set we also compared the established prognostic scoring systems to elucidate the most powerful and clinically useful statistical model. Furthermore, we sought to validate the novel CLIF-SOFA score during the first week of ICU admission within this population.

Methods

Between January 2000 and December 2010 consecutive admissions to the liver intensive therapy unit (LITU) at King's College Hospital had prospective predefined capture of baseline demographic and clinical data by dedicated auditors. The worst result/score in the 24-hour period was used for that day's result. These data were collected daily for the total critical care admission period. Detailed LITU discharge documents were produced by senior medical staff and also were used as a data source.

Patients presenting with acute liver failure, hepatocellular carcinoma, chronic liver disease not consistent with cirrhosis, and malignancy were excluded. The presence of cirrhosis was determined from clinical, biochemical, radiologic, or histopathologic results. Patients after liver transplant or transplanted during their ICU or hospital stay also were excluded. Readmissions to the ICU also were excluded from this analysis; their first ICU admission was the only one analyzed in regard to physiological parameters and eventual outcome. Elective admissions also were excluded, for example, after elective surgery or procedure.

The following organ failure definitions were used: requirement for invasive ventilation (for encephalopathy or hypoxemia, with a Pao_2/Fio_2 ratio $<$ 200 mm Hg); hypotension requiring any vasopressor support (terlipressin was not considered a vasopressor in the original SOFA score), Glasgow Coma Scale score of 9 or less; serum creatinine level of 3.5 mg/dL (or >300 μmol/L), urine output less than 500 mL/24 h, or requirement for continuous venovenous hemofiltration/renal replacement therapy; bilirubin level higher than 6 mg/dL (or 102 umol/L); and platelet count less than 50×10^9/L. Organ dysfunction/failure for the purposes of this study cohort therefore were defined as a SOFA score of 3 or higher for each of the SOFA components. Data captured on days 1, 3, and 7 of the LITU stay were used for this

analysis (see Supplementary Methods section for data that were captured).

All continuous data were tested for normality using the Kolmogorov–Smirnov test and expressed as means (SD) or medians (interquartile range) as appropriate. Comparison between continuous variables was performed using the Student *t* test or the Mann–Whitney *U* test for 2 variable comparison, and analysis of variance or the Kruskall–Wallis test for more than 2 group comparison with appropriate post hoc multiple testing correction (see the Supplementary Methods for further details on statistical modeling).

Three eras were defined for analysis within this data set: early (2000–2003), middle (2004–2007), and late (2008–2010).

Patients transferred to referring hospitals but for whom outcome data then were lost were censored at the point of hospital discharge from our institution. The De Long method was used for area under the receiver operating characteristic (AUROC) comparisons. All *P* values calculated were 2-tailed and significance was defined at the 95% level. A fixed specificity analysis was performed with sensitivity estimated using the bootstrap method (1000 iterations). Statistical analysis was performed using SPSS v16.0 (IBM, Somers, NY) and MedCalc v 11.4.1 (MedCalc Software, Mariakerke, Belgium).

Ethical approval for analysis and publication of the de-identified audit data set was given by the South East London Research Ethics Committee 3 (formerly known as the King's College Hospital Research Ethics Committee).

Results

Cohort Characteristics

A total of 1032 patients originally were identified. After exclusions, 971 patients with an underlying diagnosis of cirrhosis were admitted during the period beginning from 2000 to the end of 2011, and formed the basis of the study cohort (Table 1).

The median age was 51 years (range, 16–90 y), with a male:female sex profile of 615:356 (63%:37%). There was no survival difference between men and women and no difference in median admission APACHE II score ($P = .548$). The median admission MELD score was 23 (range, 6–40), APACHE II score was 21 (range, 5–50), and SOFA score was 10 (range, 0–19). The primary single reason for admission to the LITU was gastrointestinal hemorrhage (249 patients; 25%), followed by neurologic failure (188 patients; 19%), cardiovascular failure (102 patients; 11%), isolated renal failure (57 patients; 6%), and isolated respiratory failure (25 patients; 3%). The remainder of the cohort was admitted for multiple organ failure/septic shock (350 patients; 36%). The median number of organs in failure defined from SOFA criteria on admission was 2 (range, 0–3). The median length of LITU stay was 7 days (range, 1–236 d), and this did not change over the study period. A total of 641 patients (66%) were local patients admitted from the wards (liver wards, internal medicine wards, emergency department, and theaters/other critical care areas at King's College Hospital), with an LITU stay of 6 days (range, 1–236 d), and 330 patients (34%) were admitted as critical care transfers from other hospitals with a median LITU stay of 8 days (range, 1–156 d) ($P < .001$).

Survival

A total of 529 patients (55%) survived to LITU discharge and 465 patients (48%) survived to hospital discharge with a median survival of 91 days (Figure 1). The median length of LITU stay of a survivor was 5 days (0–136 d), and for nonsurvivors was 9 days (0–231 d) ($P < .001$). Eight patients were lost to follow-up evaluation before 90 days. Those patients with an alcoholic etiology did not have worse survival than those with other causes (survival, 251 of 520 [48%, alcohol etiology] vs 59 of 140 [42%, autoimmune] vs 54 of 120 [45%, viral hepatitis] vs 101 of 191 [53%, others]; $P = .241$; chi-square test; Figure 1).

Patients admitted primarily for management of gastrointestinal bleeding with OF had improved outcomes compared with patients admitted with organ failures of other etiology (sepsis, metabolic). The mortality rate was 78 of 249 (31%) for patients with bleeding compared with 428 of 722 (59%) for patients without bleeding as a cause for organ failure ($P < .001$). Nevertheless, 588 patients (61%) with gastrointestinal (GI) bleeding had 2 or more organs in failure by the end of day 1, but only 258 patients (26%) had 3 or more organs in failure. Although an increasing number of organs in failure in patients admitted for GI bleeding was associated with poorer survival, patients admitted for GI bleeding with 3 organs in failure at the end of day 1 still had a hospital survival rate of 50%. By comparison, patients with OF of a nonbleeding etiology had an incidence of 2 OFs of 27% and 3 OFs of 21% and a mortality rate of 56% and 75%, respectively. Over the study period, there was a nonsignificant increase in the percentage of patients with GI bleeding and organ failure ($\geq$2; 46% of all GI bleeding cases in era 1 to 57% in era 3; χ^2 for trend, $P = .09$).

Patients who had 3 OFs represent a watershed group of poor survival. Those with renal, liver, or respiratory failure as one of those OFs had worse outcomes with increased hospital mortality rate (renal, 77%; liver, 76%; respiratory, 71%) than those without (cardiovascular, 68%; cerebral, 68%; coagulation, 62%) (Table 3).

By using the definitions from the CLIF Acute-on-Chronic Liver Failure in Cirrhosis study,[18] 183 patients (9%) had an acute-on-chronic liver failure (ACLF) grade of 0 with a hospital mortality rate of 20%, 242 patients (25%) had an ACLF grade of 1 with a hospital mortality rate of 45%, 235 patients (24%) had an ACLF grade of 2 with a hospital mortality rate of 51%, and 311 patients

Table 1. Admission Data for All Included Patients and Survivors Versus Nonsurvivors

Variable	All patients (n = 971)	Survived (n = 465)	Died (n = 506)	*P* value
Age, *y*	50 (12)	47 (13)	51 (12)	.002[a]
Sex, male:female	615:356	298:167	317:189	.698[b]
Etiology				
Alcohol	520	251	269	.241[b]
Viral	120	54	66	
Autoimmune	140	59	81	
Mixed/other	191	101	90	
Reason for admission				
Bleeding	249	171	78	
Nonbleeding	722	294	428	<.001
Day 1 variables				
MAP, *mm Hg*	65 (30–156)	66 (40–155)	64 (30–156)	.004[c]
Vasopressors, yes:no	252:719	76:389	176:330	<.001[b]
HR, bpm	94 (27)	90 (26)	97 (28)	.007[a]
CVVHF,[d] yes:no	455:516	110:355	345:161	<.001[b]
Urine output *mL/d*	910 (0–5500)	1150 (0–5500)	582 (0–4000)	<.001[c]
Mechanically ventilated,[d] yes:no	558:413	249:216	309:197	.0213[b]
Fio_2, %	40 (21–100)	36 (21–100)	50 (21–100)	<.001[c]
Po_2 kPa	10.9 (3.6–44.8)	11.3 (3.6–33)	10.3 (5.5–44.8)	.001[c]
Po_2/Fio_2	208 (40–6106)	249 (40–717)	179 (41–6106)	<.001[c]
Respiratory rate, *bpm*	20 (6–68)	20 (10–43)	21 (6–68)	.013[c]
Temperature, °*C*	36.3 (1.3)	36.6 (1.1)	36.0 (1.4)	<.001[a]
WCC, $\times 10^9$/L	9.3 (0.4–77)	8.7 (1.1–68)	9.7 (0.4–77)	.011[c]
GCS	12 (3–15)	13 (3–15)	10 (3–15)	<.001[c]
Platelet level, $\times 10^9$/L	73 (1–478)	79 (1–378)	72 (5–478)	.510[c]
Bilirubin level, *μmol/L*	109 (6–1129)	55 (7–1035)	168 (6–1129)	<.001[c]
Lactate level, *mmol/L*	2.2 (0.3–24)	1.7 (0.3–12.8)	2.8 (0.6–24)	<.001[c]
pH	7.38 (6.78–7.60)	7.4 (6.9–7.57)	7.35 (6.78–7.60)	<.001[c]
HCO_3 level, *mmol/L*	20 (5)	21 (4)	19 (5)	<.001[a]
INR	1.6 (0.8–9.6)	1.4 (0.9–5)	1.8 (0.8–9.6)	<.001[c]
Creatinine level, *μmol/L*	136 (10–834)	87 (10–662)	162 (32–834)	<.001[c]
Sodium level, *mmol/L*	135 (8)	135 (7)	133 (9)	.006[a]
Albumin level, *g/dL*	24 (7)	25 (7)	24 (8)	.289[a]
APACHE II	22 (2–48)	17 (2–39)	25 (7–48)	<.001[c]
MELD	26 (3–40)	16 (3–40)	29 (6–40)	<.001[c]
SOFA	11 (2–22)	9 (2–19)	12 (2–22)	<.001[c]
CLIF-SOFA	11 (0–21)	8 (0–18)	13 (1–21)	<.001[c]
SAPS II	44 (6–102)	37(6–84)	53 (13–102)	<.001[c]

NOTE. Baseline admission data were from day 1.
CVVHF, continuous veno-venous haemofiltration; HR, heart rate; MAP, mean arterial pressure; WCC, white cell count.
[a]Student *t* test.
[b]Chi-square test.
[c]Mann–Whitney *U* test.
[d]During admission.

(32%) had an ACLF grade of 3 with a hospital mortality rate of 77% (definitions in Supplementary material).

Patients admitted as transfers from other critical care units had similar SOFA scores (median, 9; range, 1–19 vs median, 10; range, 0–18; $P = .306$), reduced admission APACHE II scores (19; range, 5–43; vs 22; range, 5–50; $P < .001$), and a reduced hospital mortality rate (46% compared with 55%; $P = .01$) compared with local admissions.

Era

Survival improved markedly over the course of the study period by defined eras (early HR, 1.00 [index]; middle, 0.595 [0.468–0.755]; late, 0.3744 [0.293–0.477]; $P < .001$ Kaplan-Meier method) (Figure 1).

During the study period the median admission APACHE II score decreased from 24 (range, 7–43) to 21 (range, 11–50; $P < .001$), and the median admission MELD score decreased from 23 (range, 6–40) to 18 (range, 6–40; $P < .001$). The difference in reduced MELD score came predominantly from the creatinine component being lower at the time of admission whereas the INR and bilirubin largely were unchanged. Over the study period, survival increases were more evident in patients with higher APACHE II scores and with greater physiological disturbances. For patients with low APACHE II scores (≤20; n = 462; 48%), there was a small but not statistically significant increase in survival

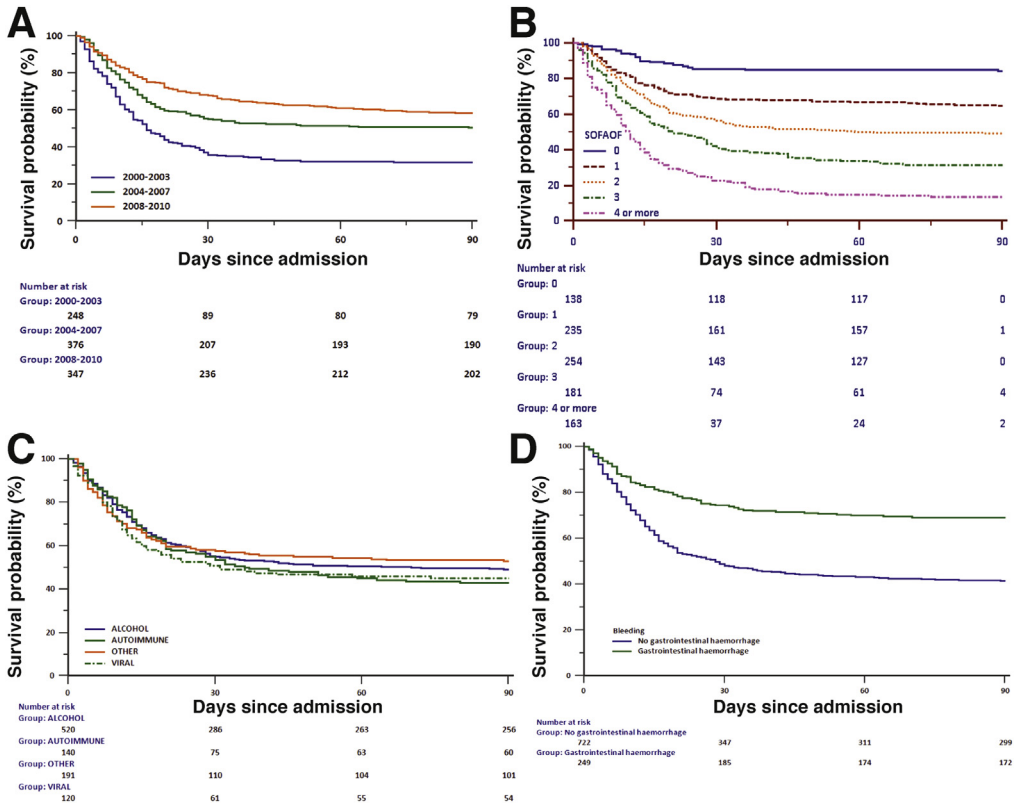


Figure 1. (*A*) Kaplan–Meier survival curves with the cohort subdivided into 3 eras: early, 2000 to 2003; middle, 2004 to 2007; or late, 2008 to 2010 ($P <$ .001 log-rank method). (*B*) Survival curves for patients with 0, 1, 2, 3, or 4 or more organs in failure (SOFA OF, SOFA score organ failure definition) on admission ($P <$ .001 log-rank method). (*C*) Survival curves for patients stratified by etiology (alcohol, viral, autoimmune, other) ($P = .328$ log-rank test). (*D*) Survival curves for patients stratified by whether gastrointestinal hemorrhage is the primary indication for admission ($P <$ .001 log-rank test).

over the study period (65% to 81%; $P = .056$), whereas for patients with APACHE II scores greater or equal to 20 (n = 509; 52%), there was a significant improvement in survival (20% to 47%; $P <$ .001) (Supplementary Results), indicating that higher survival rates were seen in the patients with more organ failures. Patients with multi-organ failure (>2 OFs) showed the largest improvement in survival rate (48% to 59% from 2000 to 2010; $P <$ .001). Excluding patients with GI hemorrhage as the primary indication for admission shows that this improvement in survival is marked in this high OF group (see Supplementary material).

Unadjusted odds ratio (ORs) for mortality change with year was 0.87 per year (0.83–0.91; $P <$ .001), and APACHE II adjusted OR for mortality was 0.89 per year (0.84–0.93; $P <$ .001). The MELD adjusted OR was 0.91 per year (0.86–0.95; $P = .002$).

Performance of Predictive Admission Scores

Of the 4 scoring systems commonly used, the admission SOFA/CLIF-SOFA score showed a modest improvement in predictive accuracy for hospital survival compared with the other systems: SOFA-AUROC, 0.799 (95% CI, 0.772–0.823), CLIF-SOFA, 0.813 (95% CI, 0.787–0.837), APACHE II, 0.768 (95% CI, 0.740–0.794), SAPS II, 0.781 (95% CI, 0.753–0.806), and MELD score, 0.789 (95% CI, 0.762–0.814) ($P = .01$ for comparison of SOFA with APACHE II, all other comparisons were $P =$ NS). A small improvement in performance was seen for predicting survival to LITU discharge: SOFA AUROC, 0.809 (95% CI, 0.783–0.834), APACHE II, 0.773 (95% CI, 0.746–0.799), SAPS II, 0.784 (95% CI, 0.757–0.810), and MELD score 0.791 (95% CI, 0.764–0.816) ($P = .005$ for comparison of SOFA with APACHE II, all other comparisons were $P =$ NS) (Table 2, Figure 2).

CLIF-SOFA showed statistical improvement compared with SOFA or other scoring systems in predicting hospital mortality (AUROC CLIF-SOFA, 0.813 [confidence interval (CI), 0.787–0.837]; $P = .015$ SOFA, $P = .010$ SAPS II, $P <$ .001 APACHE II, and $P = .023$ MELD) (see the Supplementary materials for data on other modifications of the SOFA score).

Later Testing

Prognostic models improved in their predictive accuracy for survival when calculated on day 3 with the exception of MELD score: CLIF-SOFA AUROC, 0.853 [CI, 0.827–0.876]; SOFA, 0.840 [95% CI, 0.814–0.864]; APACHE II, 0.823 [CI, 0.796–0.848]; SAPS II, 0.836 [CI, 0.809–0.860]; and MELD score, 0.795 [CI, 0.766–0.822] ($P <$ .001 for comparison of CLIF-SOFA and SOFA with MELD, and $P <$ .01 for comparison of SAPS II with MELD, all other comparisons $P =$ NS; $P = .015$ CLIF SOFA with SOFA) (Table 2, Supplementary Table 1, Figure 2).

Similarly, the predictive improvement in CLIF-SOFA and SOFA scores was greater using day 7 variables, although other scoring systems did not improve their

Table 2. Performance Characteristics of Accepted and Novel Models in the Prediction of Hospital Mortality in This Cohort at Day 1 (Admission), Day 3, and Day 7 of the LITU Stay

Model	AUROC (95% CI)	Cut-off value	Sensitivity	Specificity	PPV	NPV
Admission values						
Lactate	0.699 (0.658–0.739)	>1.9	70 (66–74)	60 (56–64)	65 (62–70)	65 (61–70)
MELD	0.786 (0.758–0.811)	>19	80 (77–84)	64 (59–68)	71 (67–75)	75 (70–79)
APACHE II	0.768 (0.724–0.806)	>20	71 (67–75)	68 (64–72)	71 (67–75)	68 (64–73)
SAPS II	0.781 (0.753–0.806)	>44	70 (66–74)	73 (69–77)	74 (70–78)	69 (65–73)
SOFA	0.799 (0.772–0.823)	>9	73 (69–77)	73 (69–77)	75 (71–78)	71 (69–75)
CLIF-SOFA	0.813 (0.787–0.837)	>11	67 (63–75)	80 (76–84)	79 (75–83)	69 (65–73)
Day 3 values						
Lactate	0.781 (0.752–0.808)	>1.8	71 (66–75)	72 (68–76)	68 (64–73)	73 (69–78)
MELD	0.784 (0.755–0.811)	>23	73 (68–77)	73 (69–77)	70 (65–75)	75 (71–79)
APACHE II	0.823 (0.796–0.848)	>20	73 (68–77)	78 (74–82)	74 (69–78)	77 (72–80)
SAPS II	0.836 (0.809–0.860)	>47	73 (69–78)	81 (77–84)	77 (72–81)	78 (74–81)
SOFA	0.840 (0.814–0.864)	>9	82 (78–86)	71 (66–75)	71 (67–75)	82 (76–85)
CLIF-SOFA	0.853 (0.827–0.876)	>10	84 (80–88)	72 (67–75)	72 (68–76)	84 (80–87)
Day 7 values						
Lactate	0.712 (0.672–0.750)	>1.8	66 (60–72)	66 (59–72)	72 (66–77)	59 (53–65)
MELD	0.764 (0.725–0.799)	>21	68 (63–74)	71 (65–77)	76 (70–81)	63 (57–69)
APACHE II	0.793 (0.756–0.827)	>20	67 (61–72)	76 (70–81)	79 (73–84)	64 (58–69)
SAPS II	0.803 (0.767–0.836)	>47	76 (71–81)	75 (69–80)	80 (75–84)	70 (64–76)
SOFA	0.844 (0.810–0.874)	>9	84 (80–88)	68 (61–73)	77 (72–82)	76 (70–83)
CLIF-SOFA	0.842 (0.808–0.872)	>10	80 (75–84)	72 (66–77)	79 (74–83)	73 (67–79)

NPV, negative predictive value, PPV, positive predictive value.

performance: CLIF SOFA AUROC, 0.842 [95% CI, 0.808–0.872]; SOFA, 0.844 [CI, 0.810–0.874]; APACHE II, 0.793 [CI, 0.756–0.827]; SAPS II, 0.803 [0.767–0.836]; and MELD score, 0.784 [CI, 0.747–0.818]) ($P < .01$ for comparison of SOFA with all other schema; all other comparisons, $P =$ NS) (Table 3).

All admission scores also were assessed for their ability to predict early (7 day) mortality, and performance was markedly lower compared with their ability to predict hospital mortality (see the Supplementary material).

Further details of logistic regression modeling and futility analysis results are in the Supplementary material.

Discussion

We have shown that in more than a decade of experience in treating patients with cirrhosis requiring organ support, clinically meaningful and statistically significant improvements in outcome have occurred. In this cohort even patients with 2 or 3 organs in failure at admission still had 30% to 55% survival rates, although the mortality rate in patients with more than 3 organs in failure at admission approached 80%.

We found that alcohol was not an etiology that was associated with worse survival compared with other causes of cirrhosis. Patients with gastrointestinal hemorrhage as a primary reason for admission did

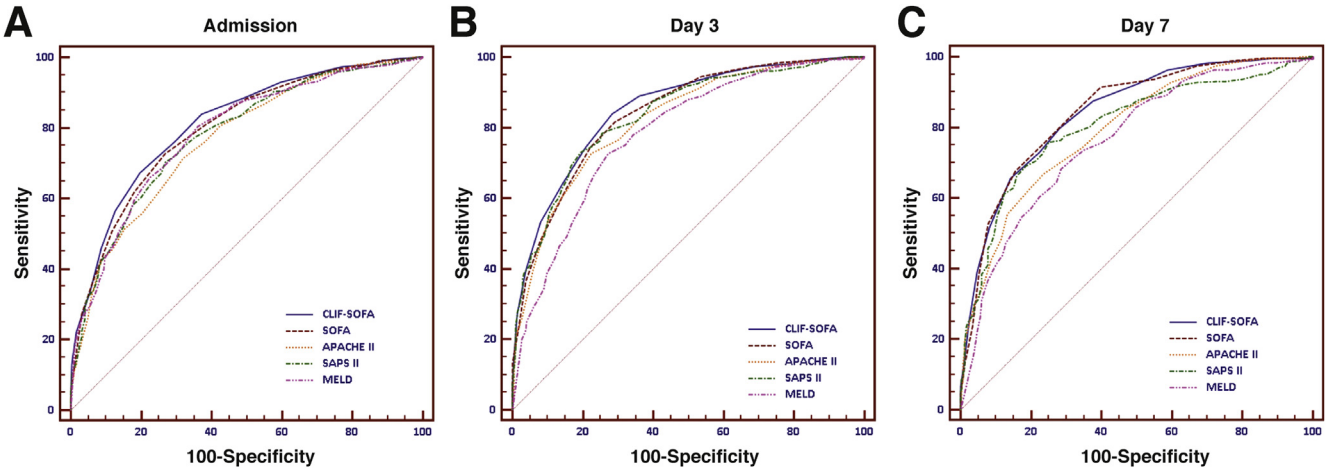


Figure 2. Comparison of receiver operating curves for the performance of CLIF-SOFA, SOFA, APACHE II, SAPS II, and MELD to predict hospital survival using variables from (*A*) admission, (*B*) day 3, and (*C*) day 7, respectively.

Table 3. Patients With 3 Organ Failures on Day 1 Stratified by the Presence of Particular Organ Failures (Defined as a SOFA Score of 3 or More)

3 organs in failure	Mortality with that organ failure	Mortality without that organ failure	*P* value[a]
Renal + 2 others	77% (69/89)	64% (59/92)	.069
Liver + 2 others	76% (62/82)	67% (66/99)	.249
Resp + 2 others	71% (91/130)	73% (37/51)	.874
CVS + 2 others	68% (53/78)	72% (75/103)	.584
Cerebral + 2 others	68% (83/122)	76% (45/59)	.333
Coag + 2 others	62% (26/42)	73% (102/139)	.215

NOTE. There was a significant trend toward higher mortality rates in patients in whom liver or renal failure made up 1 of the 3 organ failures.
Coag, coagulation.
[a]Chi-square for trend *P* value = .029.

substantially better compared with patients who were not bleeding at admission, despite associated organ failures. Universal prognostic pessimism regarding admitting patients with cirrhosis to intensive care is not justified.

We found CLIF-SOFA to be a valid stratification tool with a slight statistical improvement in prognostic discrimination over SOFA. Either score therefore could be used depending on individual unit experience without significantly impairing overall predictive accuracy. However, whether they could or should be used for individual patient decision making is debatable. In models fixing specificity at 95% we tested whether predictive accuracy was maintained, but sensitivity decreased to less than 50%, with wide confidence intervals, for both CLIF-SOFA and SOFA, suggesting they lacked the robust accuracy of a marker of futility. These scores were not designed for the purpose of deciding to withhold or withdraw organ support in individual patients but rather in describing illness severity and assessing performance between units. In individual cases they are better measures to assess response to intensive care support.[19]

Several aspects of this cohort are worthy of comment. These patients had a higher severity of critical illness compared with other published series.[5,8,17] The majority (57%) underwent invasive ventilation early in their admission whereas 47% received continuous veno-venous haemofiltration. In contrast to a recent report in a similar but smaller cohort,[20] we did not find mechanical ventilation to be of independent prognostic significance. This may be owing to our use of airway protection for patients undergoing significant variceal haemorrhage. Previous reports from the 1990s have suggested that patients with cirrhosis and 3 or more organs in failure (as defined by SOFA) at ICU admission are highly unlikely to survive.[8] Our more recent data suggest that the threshold could be increased to 4 or more because we found that patients with 3 organs in failure had a 40% survival rate. This decreased to 30% on day 3, and again we would suggest a trial of organ support is appropriate before declaring 3 OFs in these patients to be irreversible. As we have shown previously,[4] survivors have a lower cost (€8557 compared with €14,139 for all comers; $P < .001$) during their LITU admission, which is attributable in part to a shorter length of stay. Therefore, as more patients with cirrhosis survive a period of organ support, arguments suggesting critical care support is not cost effective become weaker.

The study had several weaknesses. Although data collection was predefined and prospective and primary indicators for admission may have been clear in most cases, in some there may have been secondary admission reasons that developed more importance during the critical care stay. This may not have been captured adequately in the present analysis. A small proportion of patients were repatriated to referring hospitals and therefore were lost to follow-up evaluation. Although we capped follow-up evaluation at 90 days, we could not make further comments on the long-term survival of patients with cirrhosis who survived an ICU admission at this stage.

Given our clinical interest and availability of substantial expertise within a multidisciplinary transplant team, we excluded patients transplanted within the index admission to partly mitigate any bias related to our transplant activity. However, we did not capture all data regarding transplant assessment, listing, or delisting in this cohort. Nevertheless, these data would suggest that a policy of early admission to critical care using modern organ support protocols and assessment of response at subsequent time points is eminently transferrable to all hospitals and we invite validation of our findings. Finally, we did not capture data on the continuing use of alcohol.

The improved outcomes observed likely were multifactorial and contributed to by earlier admission of patients before irreversible and progressive OF, a trend seen throughout the critical care literature. The observation, however, that outcomes also have improved specifically for those with an admission APACHE II score of higher than 20 would suggest that management techniques have improved over time for patients with cirrhosis, as well as other etiologies of chronic disease. The data we present suggest that over the eras studied patients admitted had equal severity of hepatic disease as seen by bilirubin level and INR, but lesser degrees of extrahepatic organ failures (renal) and lower rates of other organ failures as seen in decreasing APACHE II scores.

These improvements most likely reflect a general trend of attention to detail to critical care systems management (fluids, infection control, ventilation techniques, renal and cardiovascular parameters, and nutrition) and not a single new method of organ support for patients with CLD.

Patients with cirrhosis who become critically ill are a clinically challenging group of patients with a high rate of hospital mortality but with significant improvements in outcome, linked to earlier admission before multiple organ failure becomes established. Patients with

gastrointestinal hemorrhage as a primary reason for admission have improved survival rates, although no specific underlying etiology of cirrhosis is associated with poor outcome. Both the new CLIF-SOFA score or SOFA score on days 1, 3, or 7 appear to be suitable methods for outcome prediction in these patients and this study contributes to early validation of the CLIF SOFA measure. Both systems, however, are limited as indicators of futility.

Patients with cirrhosis and organ dysfunction or failure warrant a trial of critical care.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2014.08.041.

References

1. Thomson SJ, Westlake S, Rahman TM, et al. Chronic liver disease–an increasing problem: a study of hospital admission and mortality rates in England, 1979–2005, with particular reference to alcoholic liver disease. Alcohol Alcohol 2008;43:416–422.
2. Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. Gut 2005;54:1615–1621.
3. Aggarwal A, Ong JP, Younossi ZM, et al. Predictors of mortality and resource utilization in cirrhotic patients admitted to the medical ICU. Chest 2001;119:1489–1497.
4. Shawcross DL, Austin MJ, Abeles RD, et al. The impact of organ dysfunction in cirrhosis: survival at a cost? J Hepatol 2012;56:1054–1062.
5. Das V, Boelle PY, Galbois A, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. Crit Care Med 2010;38:2108–2116.
6. Arabi Y, Ahmed QA, Haddad S, et al. Outcome predictors of cirrhosis patients admitted to the intensive care unit. Eur J Gastroenterol Hepatol 2004;16:333–339.
7. Cholongitas E, Senzolo M, Patch D, et al. 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. Aliment Pharmacol Ther 2006;23:883–893.
8. Levesque E, Hoti E, Azoulay D, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. J Hepatol 2012;56:95–102.
9. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–649.
10. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.
11. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.
12. Kamath PS, Kim WR. Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology 2007;45:797–805.
13. Knaus WA, Zimmerman JE, Wagner DP, et al. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med 1981;9:591–597.
14. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957–2963.
15. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–710.
16. Berry PA, Thomson SJ, Rahman TM, et al. Review article: towards a considered and ethical approach to organ support in critically-ill patients with cirrhosis. Aliment Pharmacol Ther 2013;37:174–182.
17. Cholongitas E, Betrosian A, Senzolo M, et al. Prognostic models in cirrhotics admitted to intensive care units better predict outcome when assessed at 48 h after admission. J Gastroenterol Hepatol 2008;23:1223–1227.
18. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–1437, 37 e1–9.
19. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286:1754–1758.
20. Bahirwani R, Ghabril M, Forde KA, et al. Factors that predict short-term intensive care unit mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2013;11:1194–1200 e2.

Reprint requests
Address requests for reprints to: Julia A. Wendon, MD, FRCP, FFICM, Institute of Liver Studies, Kings College Hospital, Denmark Hill, London SE9 2RS, United Kingdom. e-mail: julia.wendon@kcl.ac.uk; fax: (44) 793279003.

Acknowledgments
All authors are grateful to the National Institute for Health Research biomedical research council at King's College London for infrastructure support during the course of this study. Mark McPhail also thanks the National Institute for Health Research biomedical research center at Imperial College London for infrastructure support during this study.

Conflicts of interest
The authors disclose no conflicts.

Funding
Supported by the Wellcome Trust (grant number ME047380MES), United Kingdom, a postdoctoral training fellowship during this study (M.J.W.M.), a doctoral studentship from the National Institute for Health Research (R.D.A.), and by a Higher Education Funding Council for England National Institute for Health Research senior lectureship (D.L.S.).

Supplementary Methods

The following data were captured: name, sex, age, date of admission, primary and secondary reason for admission, admission source, date of discharge, outcome for LITU discharge, outcome for hospital discharge, and mortality.

Further clinical data captured were as follows: diagnosis, past medical history, medication, physiological observations (heart rate, respiratory rate, blood pressure, Glasgow coma scale, oxygen saturations, daily urine output), requirement for organ support, number and type of organs supported, requirement for ventilation, requirement for cardiovascular support, requirement for renal replacement therapy, and blood test results including blood gas analysis by dedicated auditors.

It is our policy to admit patients with acute upper gastrointestinal bleeding for airway support/intubation before an endoscopy is performed if they have low-grade hepatic encephalopathy or significant bleeding. This would not count as respiratory organ failure unless the SOFA PF ratio threshold ($<$200 mm Hg) was reached. Early broad-spectrum antibiotics were given for proven or suspected infection or unexplained high-grade encephalopathy and suspected variceal gastrointestinal bleeding. Norepinephrine was the preferred initial vasopressor for hypotension refractory to intravenous fluids, with vasopressin being added as a second-line agent. Inotropic support was given using dobutamine, adrenaline, and/or milrinone in selected cases in which cardiac output was inadequate.

Renal replacement therapy was provided for support of acute kidney injury, metabolic derangement, fluid balance, and hyperammonemic encephalopathy unresponsive to medical management. Corticosteroids were used for cases of vasopressor refractory shock (noradrenaline $>$ 0.3 ug/kg/min) after a short synthetic ACTH test. Patients were defined as survivors if they left the liver ICU and subsequently were discharged home or were transferred back to the referring hospital for further rehabilitation after ward-based care and discharge from the ICU. We did not repatriate patients back to the referring intensive care unit from LITU, but as a ward-to-ward transfer.

All patients were managed following standard protocols by a multidisciplinary team in accordance with recent guidance.[19] Refusal to accept a patient for transfer was discussed among the senior clinicians but was not mandated by set criteria. Wherever possible we will not accept nonclinical transfers.

Logistic regression was used as the primary modeling tool with in-hospital mortality as the primary outcome (censored at 90 days). First, univariate assessment was performed for each variable. Adjusted (enter) multivariate analysis then was performed using age, sex, and variables associated with poor outcome in univariate mode. MELD, SOFA, APACHE II, and SAPS II were not used as variables for model building but as benchmarks to compare with models built from this data set. For this, a derivation set of approximately 50% of the entire data set was selected randomly and the remaining approximately 50% was used for model testing. Actuarial survival was calculated and comparisons between groups were made using the Kaplan–Meier method.

Results

Differential Outcome Effects of Sequential Organ Failure Assessment Subgroups

SOFA component organ failures subscores (in which a score of $\geq$3 was defined as organ failure unless modified in the CLIF Acute-on-Chronic Liver Failure in Cirrhosis study[17]) were associated with different mortality rates. For the respiratory component the mortality rate was 63%, for the cardiovascular component the mortality rate was 69%, for the renal component the mortality rate was 75%, for the cerebral component the mortality rate was 66%, and for the liver component the mortality rate was 73%. For the coagulation component, based on platelet values alone, the mortality rate was 59% and for the CLIF-SOFA component using INR the mortality rate was 75%. On multivariate analysis all SOFA organ failures had statistical significance for predicting mortality, although with differing odds ratios (renal, 3.11; 95% CI, 2.22–4.38; liver, 3.12; 95% CI, 2.25–4.33; cerebral, 2.57; 95% CI, 1.90–3.47; coagulation, 2.12; 95% CI, 1.37–3.30; respiratory, 1.95; 95% CI, 1.41–2.58; and CVS, 1.51; 95% CI, 1.05–2.16; $P < .001$ overall model).

Multivariate Analysis

A derivation cohort was determined using half of the data set (randomly generated) in preference to 2 chronologic cohorts because of the improvement in outcome during the study period. Univariate predictors of hospital mortality are shown in Table 2, with the subsequent multivariate independent predictors shown as well. De novo multivariate modeling (adjusted for age, sex, and year) on admission values generated a model based on the following admission parameters: age (OR, 1.013; 1.012–1.052), GI hemorrhage as reason for admission (OR, 0.594; 0.338–1.045), mean arterial pressure (OR, 1.013; 1.00–1.025), bilirubin (OR, 1.004; 1.002–1.005), lactate (OR, 1.617; 1.039–1;928), temperature (OR, 0.830; 0.679–0.1.014), day 1 urine volume (OR, 0.999; 0.999–0.999), requirement for renal replacement therapy (OR, 4.429; 2.653–7.394), and requirement for vasopressors (OR, 1.887; 1.031–3.420) (overall model $P <$ .001). On ROC analysis this LITU score (AUROC, 0.855; 0.820–0.855) modestly improved prediction compared with MELD (AUROC, 0.784; 0.745–0.820; $P < .001$ DeLong method), in common with SOFA (AUROC, 0.783;

0.744–0.820; $P < .001$), APACHE II (CI, 0.746; 0.724–0.806; $P < .001$), and SAPS II (CI, 0.783; 0.743–0.819; $P < .001$).

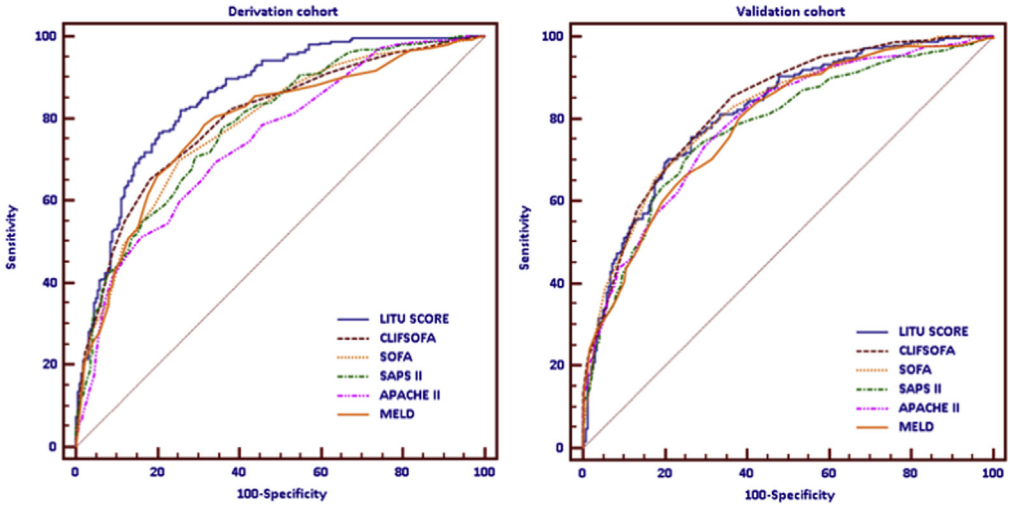
In the validation cohort the AUROC for the LITU score decreased to 0.813 (CI, 0.776–0.847), which was similar to SOFA (AUROC, 0.814; 0.776–0.847), with no statistically significant improvement for the LITU model compared with SOFA.

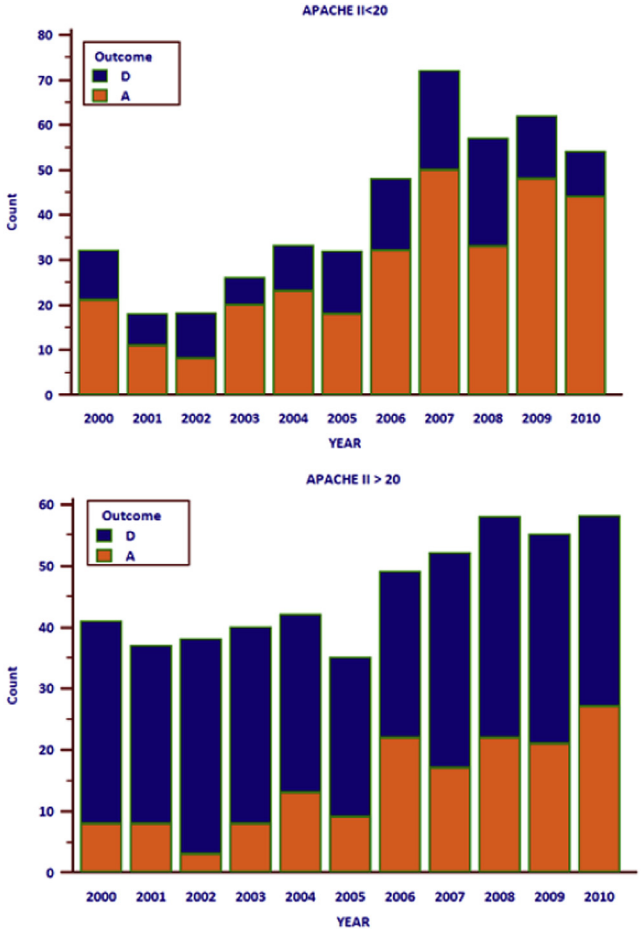
Futility Analysis

A SOFA/CLIF-SOFA score of greater than 13 on day 1 was associated with a 90% mortality rate, whereas SOFA scores greater than 13 on days 3 and 7 were associated with 89% and 90% mortality rates, respectively. A lactate level greater than 4 mmol/L on day 1 was associated with an 81% mortality rate, whereas a lactate level greater than 4 mmol/L on day 3 was associated with a 91% and an 88% mortality rate, respectively, if hyperlactatemia persisted at day 7. The absolute SOFA score on day 3 was a better predictor of mortality than change in score. If the SOFA score increased from day 1 the mortality rate was 51%, if it was unchanged it was 42%, and if it decreased it was 28%. Therefore, improvement by day 3 was a good guide to likely survival. Both the highest SOFA score and the mean SOFA score by day 3 had reduced prognostic accuracy compared with the absolute SOFA score on day 3 (AUROC [highest SOFA], 0.821; 0.793–0.847; $P = .048$ [compared with absolute], AUROC [mean SOFA], 0.831; 0.803–0.856; $P = .051$).

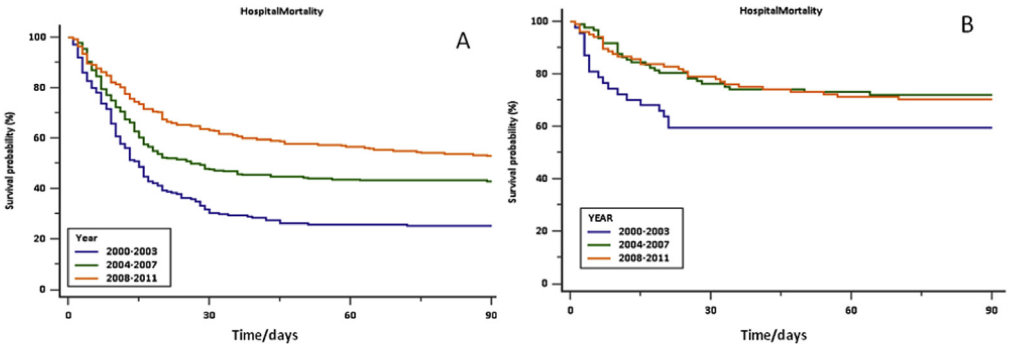
For an individual patient, nonadmission to intensive care based on a scoring system requires a low false-positive rate to prevent inappropriate prognostic pessimism resulting in a preventable death. Fixing specificity at 95% and estimating sensitivity (bootstrap method) yielded a sensitivity of 32% (26%–40%) at a cut-off value of greater than 14 for CLIF-SOFA, and 33 (26–39) at a cut-off value of greater than 12 for SOFA, suggesting neither form of SOFA score is an accurate indicator of futility.

Supplementary Figure 1. Comparison of receiver operating curves for the performance of the multivariate model from this cohort, CLIF-SOFA, SOFA, APACHE II, SAPS II, and MELD, to predict hospital survival using variables from the derivation and validation cohorts, respectively. The MV model was not a better predictor of outcome compared with SOFA/CLIF-SOFA on validation, therefore it is not presented as an alternative system.

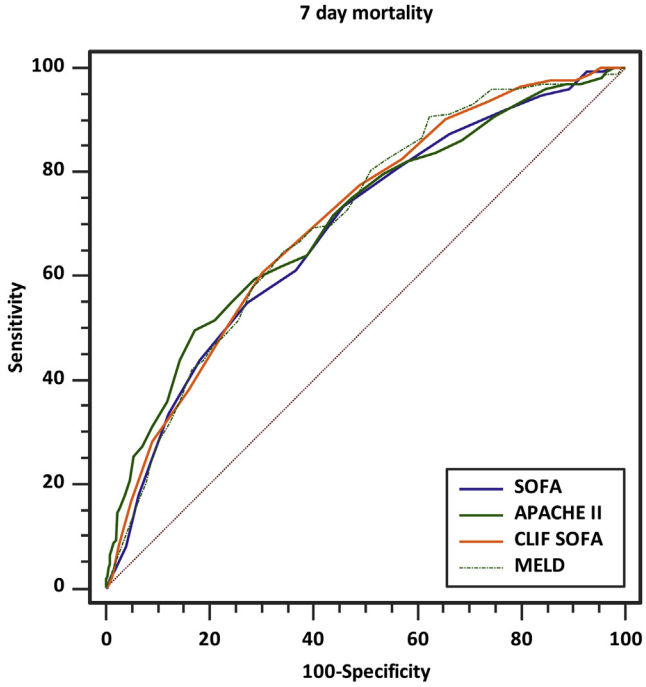




Supplementary Figure 2. Comparison of low and high admission APACHE II score subgroups on numbers admitted and hospital survival.



Supplementary Figure 3. Comparison of survival curves by era for patients (*A*) without and (*B*) with GI hemorrhage as the primary indication for LITU admission ($P < .001$, Kaplan–Meier method for both figures).



Supplementary Figure 4. ROC curve comparison between scoring systems for predicting early (7-day) mortality. No score was superior to any other and all scores performed less well than when predicting hospital mortality (SOFA AUROC, 0.687; 95% CI, 0.644–0.730; CLIF SOFA AUROC, 0.706; 95% CI, 0.663–0.744; APACHE II AUROC, 0.705; 95% CI, 0.660–0.749; and MELD AUROC, 0.703; 95% CI, 0.663–0.744).

Supplementary Table 1. Univariate and Multivariate (Enter) Logistic Regression Analysis With Hospital Mortality as the Outcome Measure

Variable	Univariate			Multivariate enter		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age	1.023	1.008–1.038	.002	1.034	1.013–1.055	.001
Sex, male:female (OR, 1)	1.080	0.746–1.562	.679	0.955	0.588–1.552	.854
Etiology			.310			
Alcohol (OR, 1)						
Viral	1.039	0.593–1.819	.892			
Autoimmune	1.255	0.740–2.128	.398			
Mixed/other	0.716	0.449–1.140	.159			
Bleeding, yes:no	0.344	0.223–0.532	<.001	0.631	0.345–1.153	.134
Year				0.852	0.788–0.933	.004
Day 1 variables						
MAP	0.986	0.980–0.998	.025	1.014	1.002–1.027	.023
Vasopressors, yes:no	3.168	2.054–4.886	<.001	1.735	0.929–3.238	.083
HR	1.010	1.004–1.017	.001			
CVVHF, yes:no	7.938	5.243–12.01	<.001[3]	4.252	2.455–7.365	<.001
Urine output	0.999	0.998–0.999	<.001	0.999	0.999–0.999	.016
Mechanically ventilated, yes:no	1.494	1.037–2.152	.030	1.098	0.600–2.011	.759
Fio_2	1.022	1.013–1.031	<.001			
Po_2	0.957	0.917–0.998	.039			
Po_2/Fio_2	0.995	0.993–0.996	<.001	0.996	0.994–0.999	.004
Respiratory rate	1.016	0.992–1.039	.173			
Temperature	0.635	0.541–0.744	<.001	0.846	0.688–1.040	.116
WCC	1.032	1.009–1.055	.003	0.998	0.971–1.026	.901
GCS	0.825	0.771–0.883	<.001	0.971	0.883–1.071	.558
Platelets	0.998	0.996–1.000	.064			
Bilirubin	1.004	1.003–1.006	<.001	1.004	1.002–1.005	<.001
Lactate	1.389	1.251–1.542	<.001	1.161	1.034–1.304	.011
pH	0.018	0.002–0.114	<.001			
HCO_3	0.900	0.863–0.936	<.001	1.013	0.954–1.075	.670
INR	1.705	1.326–2.193	<.001[2]	1.151	0.987–1.343	.071
Creatinine	1.006	1.004–1.008	<.001	1.002	1.000–1.004	.050
Sodium	0.959	0.937–0.981	.006[1]	0.983	0.951–1.015	.295
Albumin	0.997	0.953–1.001	.064	0.978	0.946–1.012	.208
APACHE II	1.150	1.114–1.187	<.001			
MELD	1.125	1.099–1.152	<.001			
MELD-Na	1.100	1.061–1.140	<.001			
SOFA	1.390	1.298–1.488	<.001			
CLIF-SOFA	1.364	1.282–1.456	<.001			
SAPS-II	1.079	1.062–1.097	<.001			
Organs in failure						
0	1					
1	2.236	0.796–6.320	.128	3.161	0.904–11.05	.071
2	4.594	1.631–12.98	.004	3.369	0.942–12.03	.061
3	8.452	2.800–25.50	<.001	4.691	1.173–18.75	.028
≥4	21.60	5.800–80.49	<.001	4.196	0.787–22.28	.092

NOTE. The c statistic for the enter multivariate model was 0.854 (95% CI, 0.819–0.884), with a Hosmer and Lemeshow *P* value of .780. For continuous variables the OR refers to the change in odds per unit change of predictor variable.

CVVHF, continuous veno-venous haemofiltration; HR, heart rate; MAP, mean arterial pressure; WCC, white cell count.

Supplementary Table 2. Day 3 (48 Hours After Admission) Data for All Included Patients and Survivors Versus Nonsurvivors

Variable	All patients (n = 849)	Survived to hospital discharge (n = 453)	In hospital mortality (n = 396)	*P* value
MAP	65 (25–134)	70 (5–134)	64 (25–123)	<.001[a]
Vasopressor, yes:no	312:537	98:355	214:182	<.001[a]
HR	97 (28–173)	83 (28–143)	100 (29–173)	<.001[a]
CVVHF	252:193	127:33	125:160	<.001[b]
Urine output	800 (0–5000)	1320 (0–4485)	200 (0–5000)	<.001[a]
Ventilation, yes:no	527:322	221:232	306:90	<.001[b]
Fio_2	35 (21–100)	30 (21–99)	40 (21–100)	<.001[a]
Po_2	10 (6–91)	10.3 (7.2–91)	10.0 (6–21)	.002[a]
Po_2/Fio_2	220 (50–2275)	249 (65–2275)	198 (49–1525)	<.001[a]
Respiratory rate	20 (8–59)	22 (8–59)	20 (8–45)	.029[a]
Temperature	36.5 (32.9–39.4)	37 (34.2–39.4)	36 (32.9–39)	<.001[a]
WCC	9.7 (0.2–52)	8.5 (0.5–32)	10.3 (0.2–52)	.002[a]
GCS	11 (3–15)	14 (3–15)	10 (3–15)	<.001[a]
HE grade	2 (-0 to 4)	2 (0–4)	2 (0–4)	.806[a]
Platelets	59 (1–353)	56 (1–353)	56 (1–294)	.022[a]
Bilirubin	115 (5–937)	58 (9–892)	165 (5–937)	<.001[a]
Lactate	1.9 (0.4–21)	1.4 (0.4–4.1)	2.3 (0.5–21)	<.001[a]
pH	7.4 (6.9–7.9)	7.4 (7.1–7.9)	7.4 (6.9–7.6)	<.001[a]
HCO3	23 (8.3–40)	23 (15–30)	23 (8–40)	.1447[a]
INR	1.6 (0.6–16)	1.4 (0.6–12)	1.8 (0.9–18)	<.001[a]
Creatinine	130 (39–581)	83 (42–412)	143 (38–591)	<.001[a]
Sodium	139 (6)	138 (6)	139 (6)	.569[c]
Albumin	21 (6)	23 (6)	20 (6)	<.001[c]
APACHE 2	21 (7)	16 (6)	23 (7)	<.001[c]
MELD	26 (5–40)	16 (5–40)	29 (6–40)	<.001[c]
SOFA	12 (2–22)	9 (2–18)	14 (4–22)	<.001[c]

CVVHF, continuous veno-venous haemofiltration; HR, heart rate; MAP, mean arterial pressure; WCC, white cell count.
[a]Mann–Whitney *U* test.
[b]Chi-square test.
[c]Student *t* test.

Supplementary Table 3. Day 7 Data for All Included Patients and Survivors Versus Nonsurvivors

Variable	All patients 533	Survived to hospital discharge 231	In-hospital mortality 302	*P* value
MAP	66 (22–133)	72 (35–133)	64 (22–127)	<.001[a]
Vasopressors, yes:no	181:352	39:192	142:160	<.001[b]
HR	100 (27–169)	93 (30–152)	100 (27–169)	<.001[a]
CVVHF, yes:no	267:266	69:162	198:104	<.001[b]
Urine output	500 (0–5170)	1401 (0–4932)	39 (0–5170)	<.001[a]
Ventilation, yes:no	363:170	119:112	244:58	<.001[b]
Fio_2	0.35 (0.21–1)	0.35 (0.21–1)	0.35 (21–100)	<.001[a]
Po_2	9.9 (5.0–45)	10 (6.8–45)	9.7 (5.0–19)	.006[a]
Po_2/Fio_2	210 (40–1018)	230 (67–1017)	192 (37–482)	<.001[a]
Respiratory rate	23 (5–61)	24 (7–49)	21 (5–61)	.035[a]
Temperature	36.8 (32.8–40.9)	37.0 (32.8–40.9)	36.0 (33.2–39.1)	<.001[a]
WCC	12 (1–61)	10 (1.8–61)	14 (1–59)	.002[a]
GCS	12 (3–15)	14 (3–15)	10 (3–15)	<.001[a]
Platelets	64 (3–721)	86 (3–559)	54 (4–721)	.041[a]
Bilirubin	137 (2–1040)	74 (2–873)	200 (2–1040)	<.001[a]
Lactate	1.9 (0.1–22)	1.5 (0.4–20)	2.2 (0.1–22)	<.001[a]
pH	7.4 (6.8–7.6)	7.4 (7.15–7.56)	7.4 (6.8–7.6)	<.001[a]
HCO_3	24.4 (5.2–34.4)	24.7 (15.7–34.4)	24.2 (5.2–34.4)	.357[a]
INR	1.6 (0.9–18)	1.4 (0.9–18)	1.8 (0.9–15)	<.001[a]
Creatinine	118 (31–583)	97 (31–421)	138 (51–583)	<.001[a]
Sodium	140 (120–157)	140 (120–155)	140 (125–157)	.469[c]
Albumin	22 (4–54)	24 (12–47)	21 (4–54)	<.001[c]
APACHE 2	20 (6–49)	17 (6–41)	23 (9–49)	<.001[c]
MELD	27 (6–40)	19 (6–40)	31 (6–40)	<.001[a]
SOFA	11 (1–18)	8 (2–16)	13 (1–18)	<.001[a]

CVVHF, continuous veno-venous haemofiltration; HR, heart rate; MAP, mean arterial pressure; WCC, white cell count.
[a]Mann–Whitney *U* test.
[b]Chi-square test.
[c]Student *t* test.

Supplementary Table 4. Accuracy of Outcome Prediction for SOFA Score and Variations

Model	AUROC (95% CI)	Cut-off value	Sensitivity	Specificity	PPV	NPV
Admission values						
SOFA	0.799 (0.772–0.823)	>9	73 (69–77)	73 (69–77)	75 (71–78)	71 (69–75)
CLIF-SOFA	0.813 (0.787–0.837)	>11	67 (63–75)	80 (76–84)	79 (75–83)	69 (65–73)
SOFA+lactate	0.807 (0.781–0.832)	>12.4	70 (66–74)	77 (73–81)	77 (73–81)	71 (66–75)
SOFA - bilirubin	0.764 (0.735–0.790)	>7	63 (59–67)	76 (72–80)	74 (70–78)	66 (61–70)
SOFA - platelets	0.799 (0.772–0.822)	>7	75 (71–79)	69 (75–73)	73 (69–76)	72 (67–75)
Day 3 values						
SOFA	0.840 (0.814–0.864)	>9	82 (78–86)	71 (66–75)	71 (67–75)	82 (76–85)
CLIF-SOFA	0.853 (0.827–0.876)	>10	84 (80–88)	72 (67–75)	72 (68–76)	84 (80–87)
SOFA+lactate	0.865 (0.840–0.887)	>11	87 (83–90)	70 (66–74)	72 (67–76)	86 (82–89)
SOFA - bilirubin	0.819 (0.791–0.844)	>7	76 (71–80)	74 (69–78)	72 (67–76)	78 (73–81)
SOFA - platelets	0.847 (0.821–0.871)	>7	86 (82–89)	69 (65–74)	71 (67–76)	85 (81–88)
Day 7 values						
SOFA	0.844 (0.810–0.874)	>9	84 (80–88)	68 (61–73)	77 (72–82)	76 (70–83)
CLIF-SOFA	0.842 (0.808–0.872)	>10	80 (75–84)	72 (66–77)	79 (74–83)	73 (67–79)
SOFA+lactate	0.846 (0.813–0.876)	>10.4	90 (86–93)	63 (57–70)	76 (72–81)	83 (76–88)
SOFA - bilirubin	0.823 (0.788–0.854)	>7	77 (72–81)	76 (69–81)	81 (76–85)	72 (66–77)
SOFA - platelets	0.834 (0.799–0.864)	>8	74 (69–79)	76 (71–82)	81 (75–85)	69 (63–75)

NOTE. Parentheses indicate 95% confidence intervals.
NPV, negative predictive value; PPV, positive predictive value; SOFA+lactate, SOFA score plus serum lactate; SOFA-platelets, SOFA score minus platelets component; SOFA-bilirubin, SOFA score minus bilirubin component.

Supplementary Table 5. SOFA and CLIF SOFA Definitions

CLIF - SOFA Organ system	0	1	2	3	4
Liver, bilirubin, *mg/dL*	<1.2	≥1.2 to ≤2.0	≥2.0 to ≤6.0	≥6.0 to <12.0	≥12.0
Kidney, creatinine, *mg/dL*	<1.2	≥1.2 to ≤2.0	≥2.0 to ≤3.5	≥3.5 to <5.0 or RRT	≥5.0 or RRT
Coagulation, INR	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	≥2.5 or platelet count ≤ 20 $\times 10^9$/L
Circulation, mean arterial pressure, mm Hg	≥70	<70	Dopamine ≤5 or dobutamine or terlipressin	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Respiratory					
Pao_2/Fio_2	>400	>300 to ≤400	>200 to ≤300	>100 to ≤200	≤100
Spo_2/Fio_2	>512	>357 to ≤512	>214 to ≤357	>89 to ≤214	≤89
Cerebral	No HE	I	II	III	IV

SOFA Organ system	0	1	2	3	4
Liver, bilirubin *mg/dL*	<1.2	≥1.2 to ≤2.0	≥2.0 to ≤6.0	≥6.0 to <12.0	≥12.0
Kidney, creatinine, *mg/dL*	<1.2	≥1.2 to ≤2.0	≥2.0 to ≤3.5	≥3.5 to <5.0	≥5.0
Coagulation, platelets $\times 10^9$/L	>150	>100 to ≤150	>50 to ≤100	>20 to ≤50	≤ 20
Circulation, mean arterial pressure, *mm Hg*	≥70	<70	Dopamine ≤5 or dobutamine	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Respiratory Pao_2/Fio_2	>400	>300 to ≤400	>200 to ≤300	>100 to ≤200	≤100
Cerebral, GCS	15	13–14	10–12	6–9	<9

NOTE. Doses of dopamine/dobutamine/E/NE are shown in μg/kg/min.
E, epinephrine; NE, norepinephrine; RRT, renal replacement therapy; Spo_2, pulse oximetric saturation.