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THE UTILITY OF SCORING SYSTEMS IN CRITICALLY ILL CIRRHOTIC PATIENTS ADMITTED TO A GENERAL ICU.

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Introduction

Liver disease is a serious public health issue in the UK[1]. Scotland in particular has cirrhosis mortality rates double that of the European average. [2]. Liver disease predisposes the patient to numerous complications and they are at an increased risk of critical illness[3]. Admissions with cirrhosis doubled in the UK between 2003 and 2008. This is likely to increase further [4, 5].

Admissions with cirrhosis have a high mortality with Thomson et al reporting a mortality rate of 45%. [5]. With each additional failing organ system, ICU mortality rates increase. [6]. Renal failure and sepsis with cirrhosis are associated with particularly poor outcomes[7]. This poor prognosis has led to questions regarding the admission of some of these patients to ICU[4].

It is becoming increasingly important to be able to identify who might benefit from admission to the ICU. A number of different scoring tools have been used for this purpose[8]. Most studies are from Asia or from transplant centres [9]. These centres have a different case mix of cirrhotic patients compared to the general ICU [4, 10, 11]. More data is needed from the non-transplant setting to establish whether evidence from the these specialist centres is transferrable to the general ICU, where a high proportion of critically ill cirrhosis patients are treated[12]

The aim of the present study was to examine the characteristics of a cohort of critically ill patients with cirrhosis who were admitted to a general ICU over a 12 month period. **We aimed to analyse the utility of prognostic scoring tools in these patients and to identify whether liver specific or general ICU scoring tools have a greater discriminative ability**. In addition, we identified any independent predictors of mortality.

Materials and Methods

This study was approved by the Local Research Ethics Committee; *(West of Scotland Research Ethics Committee 5, approved 20th March 2012, REC reference; 12/WS/0039.)* Data was collected prospectively over a period of 12 months (June 2012 to May 2013) from the Glasgow Royal Infirmary (GRI) ICU. The ICU has 20 critical care beds and is a mixed surgical / medical unit, affiliated with the University of Glasgow. The ICU does not offer a dedicated hepatology critical care service and the hospital does not offer tertiary liver transplant services.

Patients

All ICU admissions at the GRI between June 2012 and June 2013 had their records screened for a diagnosis of cirrhosis. ICU patients were defined as those referred to and accepted for level 3 care.

This involves requiring advanced respiratory support or basic respiratory support together with the support of at least two organ systems[13].

Cirrhosis was diagnosed either histologically or via clinical suspicion. Clinically, a patient was deemed cirrhotic if they had features of chronic liver disease with evidence of portal hypertension, ascites, encephalopathy or a liver-spleen scan consistent with cirrhosis. An independent clinician verified the diagnosis of cirrhosis. Only patients over the age of 18 were included in the study.

Methods

Clinical and demographic data were collected prospectively via the patient record (CareVue, Philips Medical Systems, Eindhoven, The Netherlands) upon admission to the unit to allow the calculation of the different scoring systems. Demographic data collection included: *Age, gender, aetiology of cirrhosis, primary diagnosis on ICU admission and Scottish Index of Multiple Deprivation (SIMD) category*. Clinical data collected on admission included: *Sodium, potassium, bilirubin, creatinine, urine output (at 6, 12 and 24hrs), weight, urea, lactate, white cell count (WCC), platelets, PT ratio, albumin,* PaO_2*:*FiO_2 *ratio, mean arterial pressure (MAP), inotrope dose, pre-intubation encephalopathy / Glasgow Coma Score (GCS) and ascites grade*. Additional variables were collected at 72hrs to enable the Sequential Organ Failure Assessment (SOFA) score[14] and Acute Kidney Injury Network (AKIN) score[15] to be calculated on day 3 of admission. This electronic database is validated and complete[16].

Encephalopathy grade (and GCS) was assigned pre-intubation according to the West Haven Criteria[17] by the admitting clinician. The ascites grade was assigned according to the International Ascites Club definition[18].

Patients were further categorised according to organ failure status. These were categorised into any combination of renal, cardiovascular, respiratory, or no failing organs. A patient was deemed to have failing kidneys if they required renal replacement therapy (RRT), cardiovascular failure if they required inotropic or vasopressor support, and respiratory failure if they needed mechanical ventilation.

Outcome data was obtained via electronic records and no further patient follow up occurred. No patients were lost to follow up.

Scoring systems

Eight scoring tools were analysed initially. Liver specific scoring tools included the Child-Turcotte-Pugh (CTP)[19], the Model for End-stage Liver Disease (MELD)[20], and the UK End-stage Liver Disease model (UKELD)[21]. The CTP score has been in use for a number of years, whereas MELD and UKELD are more recent scores and are predominantly used in the transplant setting. The Glasgow Alcoholic Hepatitis Score (GAHS)[22] was included based on recent evidence from Thomson et al suggesting it might be of use in a critical care setting[5]. The Acute Physiology and Chronic Health Evaluation II (APACHE II)[23] score and the Sequential Organ Failure Assessment (SOFA)[14] scores are routinely used, and they were the general ICU scores that we analysed. The Acute Kidney Injury Network score (AKIN) is a renal specific score in routine use to assess kidney injury[15]

The Chronic Liver Failure – Sequential Organ Failure Assessment (CLIF-SOFA) score[24] is an adaption of the SOFA score, and has been recently developed as part of a large multi-centred study investigating acute on chronic liver failure[24].

SOFA and AKIN scores were calculated at 72 hours to allow us to investigate whether their prognostic accuracy differs after patients have been subject to three days of intensive care treatment.

Statistical analysis

Normally distributed data are reported as mean ± standard deviation. Student's t-test was used to compare parametric data. Non-normally distributed continuous variables are reported as median (interquartile range) and were compared using the Mann-Whitney U-test. Proportions were compared using a chi-square test or Fisher exact test if required. Significance testing was two sided and deemed significant if $p < 0.05$.

Multivariate, backward, stepwise logistic regression analysis was performed on selected significant variables to identify any independent factors associated with mortality.

All scoring tools were compared using receiver operator characteristic (ROC) curves. The area under the curve (AUC) provided the discriminative ability of the score. Optimum cut-off points were selected by the investigators based on the most clinically applicable sensitivity and specificity values.

All analysis was performed using SPSS. (SPSS Inc, IBM, Chicago, Illinois, USA v.18.) Statistical advice was provided by an independent statistician.

Results

62 patients were admitted to the ICU over the 12 month period. Upon independent verification of cirrhosis, three patients were excluded as definitive evidence of cirrhosis could not be confirmed. This left a cohort of 59 critically ill cirrhosis patients. Patient characteristics are shown in Table 1. The mean age was 51 ± 12 years, 40 (68%) were male, and alcohol was the main cause of cirrhosis (80%). The most common primary diagnoses on admission were respiratory failure (39%), and gastro-intestinal bleeding (16%). ICU and hospital mortality were 31% and 48% respectively.

Risk factors for mortality: Univariate analysis

Table 1 also shows the results of the univariate analysis of variables associated with ICU mortality. There was no significant difference in age (*p = 0.451*), cause of cirrhosis (*p = 0.466*), reason for admission (*p =0.437*) or deprivation status (*p = 0.275*). Patients who died during their stay in the ICU had significantly higher prognostic scores in all scores other than in AKIN (CTP, MELD, UKELD, GAHS, APACHE II, SOFA and CLIF-SOFA).

Of the clinical variables, bilirubin and PT ratio were significantly associated with ICU mortality (*p = 0.007 and 0.02 respectively*). Lactate and the presence of ascites were also significantly associated with mortality (*p < 0.001 and p=0.021* respectively). Interestingly acute kidney injury (AKI) and encephalopathy were not significantly associated with ICU mortality (*p = 0.598 and 0.151* respectively).

Multivariate analysis

A multivariate, backward stepwise logistic regression analysis was undertaken to identify any independent factors in determining ICU outcome. Prognostic scores were not included in this analysis as this study aimed to establish individual risk factors. The results are given in Table 2 showing that lactate and ascites on admission are independent predictors of ICU mortality. These gave odds ratios of 1.69 and 5.91 respectively. Both are statistically significant with *p = 0.008 and 0.018.*

Lactate

This study adds to the accumulating body of evidence that serum arterial lactate is an independent predictor of mortality[25–28]. We therefore analysed the incorporation of lactate into scoring models. The CTP score was chosen as the model in which lactate would be incorporated because of its relative simplicity and ease of calculation. It can be calculated at the bedside without the need of a calculator or a computer programme, unlike MELD, UKELD, APACHE II and SOFA / CLIF – SOFA. Burroughs et al[26] have also recommended the incorporation of lactate into the CTP score.

Our two alterations to the CTP score, provisionally termed CTP – L and CTP + L can be found in Table 3. The CTP – L involves the insertion of a new category: Lactate. As with the previous five categories we assigned a score ranging from 1 to 3. An admission lactate of < 2 mmol/l gave a score of one, of 2.0 – 4.0 mmol/l gave a score of 2, and > 4.1 mmol/l gave a score of three. These three lactate cut-off values were chosen based on commonly reported cut-off values in intensive care settings[29]. The minimum available CTP-L score is therefore 6, with the maximum being 24.

The second alteration was termed the Child-Turcotte-Pugh + Lactate score (CTP + L). In this, we took the overall CTP score for a patient (with no defined units) and simply added the admission serum lactate (mmol/l) onto this score. We removed any units assigned to the numbers, and this produced the new score. The CTP + L is therefore continuous, with the minimum score possible being 5, and the maximum being limited by the physiological range of serum lactate.

ROC curve analysis

ROC curves for all scores analysed are presented in Table 4. Of the established scoring tools, SOFA performed the best, with an AUC of 0.76 (0.64 – 0.89), with CLIF-SOFA producing a similar AUC of 0.75 (0.62 – 0.88). All the scores performed to a similar standard of between 0.70 and 0.76 (other than AKIN), although none reached the clinically useful AUC level of 0.8[30]. The AKIN score performed poorly with an AUC of 0.52 (0.35 – 0.69).

37 patients remained in the ICU at 72 hours post admission. Of the 22 who were not in the unit at 72 hours, 9 had died and 13 had been discharged to other areas. Both the SOFA and AKIN scores at 72 hours performed very similarly to the score at 0 hours.

The AUC for the two CTP alterations to incorporate lactate (CTP-L and CTP + L) are also shown in Table 4. **The incorporation of lactate improved the discriminative ability of the scores, with the CTP-L producing an AUC of 0.78 (0.64 – 0.91)**. The CTP + L improved further and produced the highest AUC of any score, with an AUC of 0.86 (0.75 – 0.97). The ROC curves of the CTP, CTP-L and the CTP+L are presented in Figure 1.

Discussion

This one year prospective cohort study has evaluated the outcome of 59 consecutive patients with cirrhosis admitted to a large, general ICU in the UK. 18 of these patients died in the unit, giving an

ICU mortality of 31% over the period of June 2012 to May 2013. This compares favourably to the literature in which a weighted ICU mortality of 45% has been reported[31].

The primary outcome of this study was that SOFA was the best performing prognostic tool of the established scoring systems in critically ill cirrhosis patients admitted to a general, non-transplant ICU. **The study also identified that lactate and ascites were independent predictors of ICU mortality, and that the incorporation of lactate into the CTP, (via the CTP + L score) improved its discriminative ability.** This contrasts with the other scores analysed, none of which reached the clinically useful threshold AUC of 0.8[30].

The 31% mortality rate in this study is lower than reported in a review of the literature by Flood et al[31]. This reflects the trend towards improved outcomes of these patients over time[32], and compares to the 38% and 39% recently reported from two studies in British non-transplant ICUs[5, 10]. A likely explanation for the low mortality rates may be the comparative low degree of hepatic dysfunction seen in our patients. 47% (28/59) were classified as Child-Pugh category C, and the median MELD score was 18. Both of these indicators of hepatic disease severity are the lowest of any published paper in this area. As in other studies from non-transplant centres [6] this is likely to be a result of local referral patterns and the associated selection bias.

The prognostic effect of AKI on critically ill patients with liver cirrhosis has been extensively investigated [7, 28, 33, 34]. It has been established that it is associated with a poor prognosis, with Cholongitas et al[28] quoting 71% to 91% ICU mortality depending on the severity of AKI. This was not seen in the present study, where there was no significant relationship between AKI on admission and ICU mortality *(p = 0.598).* This may have been caused by a heavy selection bias resulting from local referral patterns within the hospital. Critically ill cirrhosis patients with AKI are only likely to be admitted to the ICU if it was believed they had a realistic chance of survival. Patients with a reversible precipitating factor are more likely to be referred for level 3 care. Those without a reversible precipitating factor tend to be managed at ward level. This relates to an important paper by Martin-Llahi et al in which they show that the cause of renal failure is of importance in patients with cirrhosis[35]. It is possible that patients in the present study had a more benign and transient form of AKI because of their lower degree of hepatic dysfunction and the heavy selection bias. This is logical and may explain the comparative low ICU mortality rates, and the low prognostic ability of the scoring systems, many of which have a renal function component.

Of the established scoring tools, the SOFA score had the best discriminative ability, with an AUC of 0.76, this is consistent with much of the literature[36–39] and is to be expected in our cohort who

seem to be admitted to the ICU *with* cirrhosis rather than because of their cirrhosis. **The relatively low discriminative ability of the scores is consistent with the limited amount of literature from a non-transplant setting[5, 10, 26] and this paper supports the evidence suggesting that scoring tools should not be used independently in deciding who should be admitted to the ICU in a non-transplant setting.**

Lactate and ascites were independent predictors of ICU mortality in our patient cohort. Lactate produced a statistically significant odds ratio of 1.69, and when incorporated into the CTP score to produce the CTP + L score produced an AUC of 0.86. A cut-off point of >14 produces a sensitivity of 78% and a specificity of 98%, which suggests that it is of more clinical use than the other scores analysed. An AUC of 0.86 is the greatest of any score identified from within a non-transplant critically ill cirrhosis cohort. **As well as being the best discriminative score so far observed, the CTP + L score is not a major revision of the CTP score. It remains simple, quick and easy to calculate at the bedside – a factor considered important by the authors**. The serum arterial lactate is routinely collected in the ICU, and can be collected on the wards. **A simple addition of the lactate level in mmol/l into the CTP score produces the CTP + L score and provides clinicians with clinically useful scoring tool.** Although the CTP + L score requires extensive validation in different ICU cirrhosis cohorts before it can be used with confidence, this study suggests that clinicians should analyse serum arterial lactate levels when triaging critically ill patients with cirrhosis.

For the first time, the link between deprivation and patients admitted to the ICU with cirrhosis has been investigated. Although deprivation was not associated with ICU outcome ($p = 0.275$), the majority of patients (81%) in this study were in the bottom two most deprived quintiles of society. This has been suspected for a number of years, but this study has provided some quantification.

This study provides information on the impact of organ failure on ICU outcome, the utility of scoring tools in a general ICU setting, and it has also put forward a potential new way of stratifying these patients – the CTP + L score. The prospective nature of the study means that pre-intubation encephalopathy and GCS scores could be obtained**. This means that certain scores such as SOFA and CTP are likely to be more robust than in previous studies**, which have listed the inability to obtain pre-intubation encephalopathy scores as a significant limitation [5].

The 12 month study period allowed us to recruit 59 patients, which is a lower number than previous papers[5, 38, 39]. The prospective methodology does however provide us with reliable information regarding how many of these patients present to a general, non-transplant ICU over a one year period. It provides us with contemporary data that is applicable to a large number of clinicians, and

adds to the much needed, limited body of evidence regarding these patients in a non-transplant setting. **Further work is ongoing to extend the sample size which will allow the authors to investigate fully how best to integrate lactate into a scoring tool.**

In conclusion, this year long, prospective study of critically ill cirrhosis patients admitted to a general ICU has identified lower than expected ICU mortality. In contrast to the literature, AKI was not as negative a prognostic marker as previously reported. The SOFA score was the best performing prognostic tool, but none of the scores performed to a clinically useful level. **Lactate and ascites were independent predictors of ICU mortality, and when lactate was incorporated directly into the CTP score to produce the CTP + L score, its discriminative ability increased to a level whereby it may be of clinical use.**

Table and figure legends

Table 1.

Clinical characteristics and predictive factors of ICU mortality determined by univariate analysis in 59 cirrhosis patients admitted to a general ICU. Data are displayed as mean ± standard deviation, median (interquartile range). Categorical data is reported as within group number and (%).

Table 2.

Odds ratios of variables remaining in the multivariate regression model.

Table 3.

The methodology of calculating the CTP-L and CTP + L scores.

Table 4.

The area under the curves, cut off points, sensitivity and specificity and optimum cut-off points of the prognostic scoring tools analysed.

Figure 1.

The Receiver Operator Characteristics curves (ROC curves) of the CTP, CTP-L and CTP + L scores.

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	All patients (n=59)	ICU Survivors (n=41)	ICU Non-survivors (n=18)	*P value*
Age (years)	51 ± 12	50 ± 12	52 ± 12	0.451
Gender (male)	40 (68%)	27 (66%)	13 (72%)	0.435
Cause of cirrhosis n(%)				0.466
Alcohol	47 (80%)	32 (78%)	15 (83%)	
Non-alcoholic	12 (20%)	9 (22%)	3 (17%)	
Length of stay (days)	5 (42)	5 (32)	4 (42)	0.167
Reason for ICU admission				0.437
Respiratory failure	23 (39%)	16 (39%)	7 (39%)	
Gastrointestinal bleed	10 (16%)	6 (15%)	4 (22%)	
Encephalopathy	5 (9%)	4 (10%)	1 (5%)	
Sepsis	5 (9%)	2 (5%)	3 (17%)	
Other	16 (27%)	13 (31%)	3 (17%)	
Number of organs requiring support				0.017
0	1 (2%)	0 (0%)	1 (5%)	
1	17 (28%)	16 (39%)	1 (5%)	
2	30 (51%)	20 (48%)	10 (56%)	
3	11 (19%)	5 (12%)	6 (34%)	
Prognostic scores on ICU admission				
APACHE II	22 (16-27)	19 (15-24)	23 (21-33)	0.009
Child-Pugh	9 (7-12)	9 (7-11)	11.5 (9-13)	0.013
MELD	18 (8-23)	13 (7-21)	21 (19-32)	0.003
AKIN	0 (0-2)	0 (0-2)	0 (0-2)	0.791
UKELD	51 (48-57)	51 (47-53)	58 (50-62)	0.015
GAHS	7 (6-9)	7 (6-8)	8.5 (7-10)	0.004
SOFA	10 (8-12)	9 (6-11)	11 (10-14)	0.001
CLIF-SOFA	10 (10-12)	9 (9-11)	11.5 (10-14)	0.002
Clinical parameters				
AKI	20 (34%)	14 (34%)	6 (33%)	0.598
Ascites	26 (44%)	14 (34%)	12 (67%)	0.021
Encephalopathy	19 (32%)	11 (27%)	8 (44%)	0.151
Biological parameters on admission				
Sodium (mmol/l)	137 ± 6	137 ± 6	136 ± 6	0.534
Creatinine (µmol/L)	124 ± 89	112 ± 77	152 ± 108	0.117
Bilirubiin (µmol/L)	91 ± 109	67 ± 86	148 ± 134	0.007
PT ratio	1.7 ± 0.7	1.6 ± 0.5	2.0 ± 0.9	0.02
Lactate (mmol/l)	2.9 ± 3.4	1.8 ± 1.3	5.5 ± 5.1	<0.001
Urea (mmol/L)	10.1 ± 7.8	10.1 ± 8.5	10.5 ± 6.2	0.846
WBC (10^9/L)	14.0 ± 8.2	13.7 ± 7.4	14.8 ± 10.0	0.638
Platelets (10^9/L)	130 ± 85	143 ± 89	102 ± 75	0.094
Albumin (g/L)	20 ± 6	20 ± 6.3	20 ± 6.5	0.932
Potassium (mmol/l)	4.2 ± 0.85	4.1 ± 0.9	4.3 ± 0.8	0.481

PaO2:FiO2 ratio	25.9 ± 19.3	27.4 ± 20.3	23.1 ± 17.7	0.447
Deprivation (SIMD category)				0.275
1-2 (deprived)	48 (81%)	32 (78%)	18 (89%)	
3-5 (non-deprived)	11 (19%)	9 (22%)	2 (11%)	
Hospital mortality	28 (48%)			
ICU mortality	18 (31%)			

APACHE II, Acute Physiology And Chronic Health Evaluation II score, PT ratio; Prothrombin Time ratio, SOFA; Sequential Organ Failure Assessment.
MELD; Model for End-stage Liver Disease, UKELD; UK Ens-stage Liver Disease model, ICU; Intensive Care Unit, WBC; White Blood Count
AKIN; Acute Kidney Injury Network score, AKI; Acute Kidney Injury, GAHS; Glasgow Alcoholic Hepatitis score, SIMD; Scottish Index of Multiple Deprivation.

Table 1. Clinical characteristics Predictive factors of ICU mortality determined by univariate analysis in 59 cirrhosis patients admitted to a general ICU.

Variable	Odds Ratio	95% C.I.	*P value*
Lactate	1.69	1.15 - 2.49	*0.008*
Ascites	5.91	1.35 - 25.88	*0.018*

Table 2. Odds ratios of variables remaining in the multivariate regression model.

The Child-Turcotte-Pugh - Lactate score (CTP - L)

Variable	1 point	2 points	3 points
Bilirubin (µmol/l)	< 34	34-50	> 50
Albumin (g/l)	> 35	28 -35	< 28
INR (or PT ratio)	< 1.7	1.71 -2.30	>2.3
Lactate (mmol/l)	**< 2.0**	**2.1 -4.0**	**> 4.1**
Ascites	None	Mild	Severe
Hepatic Encephalopathy	None	Grade I / II	Grade III / IV

The Child-Turcotte-Pugh + Lactate score (CTP+L)

Variable	1 point	2 points	3 points
Bilirubin (µmol/l)	< 34	34-50	> 50
Albumin (g/l)	> 35	28 -35	< 28
INR (or PT ratio)	< 1.7	1.71 -2.30	>2.3
Ascites	None	Mild	Severe
Hepatic Encephalopathy	None	Grade I / II	Grade III / IV
Serum arterial lactate	**Addition to overall score gained from above categories**		

The overall CTP score is calculated according to the five criteria above. THE CTP + L score is calculated via the addition to this score of the serum arterial lactate level **in mmol/l.** Once done, any units associated are removed, to give an overall, continuous score.

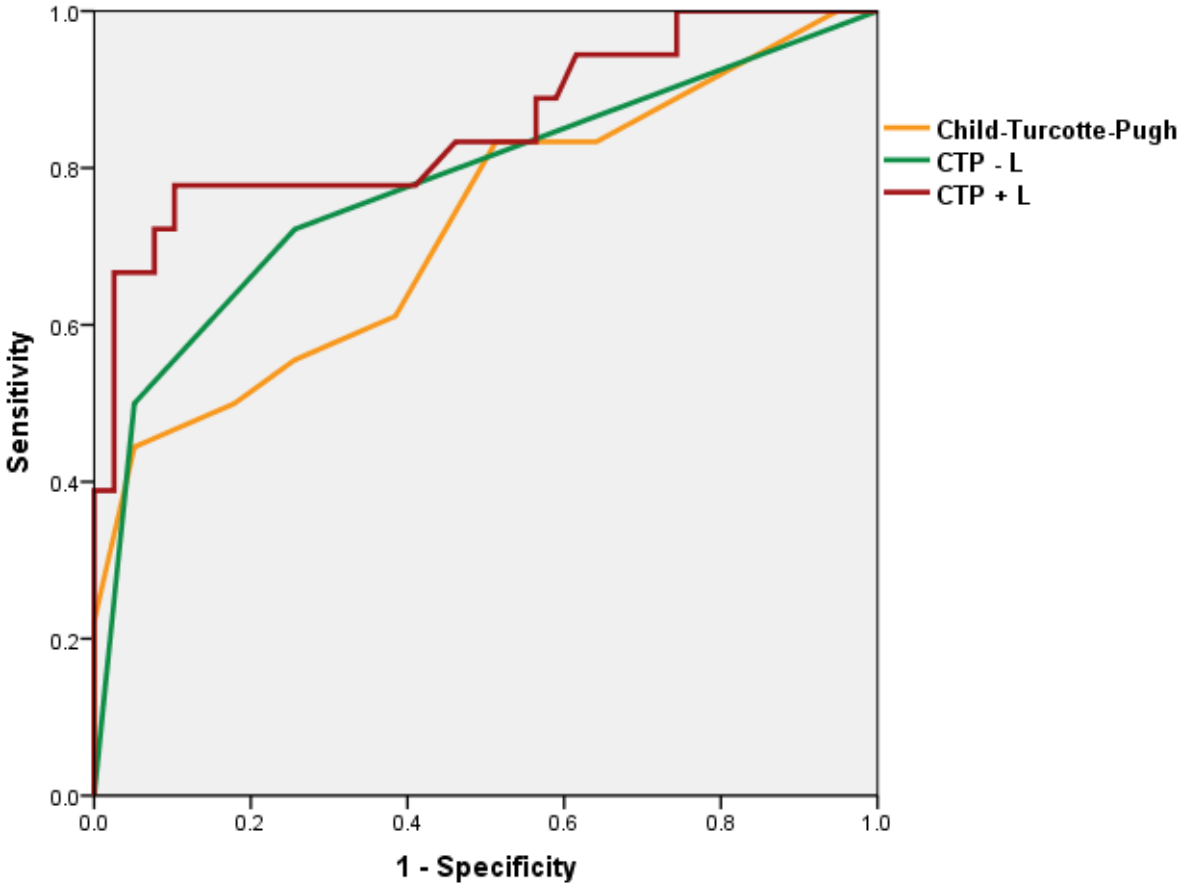
Table 3. The methodology of calculating the CTP-L and CTP + L scores.

Scoring system	AUC	95% C.I.	Cut-off point	Sens (%)	Spec (%)
Established liver specific scoring systems					
Child-Turcotte-Pugh **(CTP)**	0.7	0.55 - 0.85	9.5	61	62
Glasgow Alcoholic Hepatitis Score (**GAHS**)	0.73	0.59 - 0.87	7.5	67	66
Model for End-stage Liver Disease (**MELD**)	0.74	0.61 - 0.88	18	83	67
UK Model for End-stage Liver Disease (**UKELD**)	0.7	0.55 - 0.85	54	61	97
Established general ICU scoring systems					
Acute Physiology And Chronic Health Evaluation II (**APACHE II**)	0.72	0.58 - 0.85	22	61	68
Sequential Organ Failure Assessment Score (**SOFA**)	0.76	0.64 - 0.89	10.5	72	69
Renal specific scoring tool					
Acute Kidney Injury Network score (**AKIN**)	0.52	0.35 - 0.69	2.5	22	93
Proposed scoring system					
CLIF - SOFA	0.75	0.62 - 0.88	10.5	83	59
72 hour scores					
72 hour SOFA	0.74	0.57 - 0.90	10.5	78	68
72 hour AKIN	0.52	0.30 - 0.75	2.5	22	85
Novel scoring systems proposed in this paper					
CTP-L	0.78	0.64 - 0.91	11.5	72	68
CTP + L	0.86	0.75 - 0.97	14	78	90

AUC; Area Under the Curve. CTP-L; Child-Turcotte-Pugh with lactate. CTP + L; Child-Turcotte-Pugh + Lactate
Sens; Sensitivity, Spec; Specificity

Table 4. The area under the curves, cut off points, sensitivity and specificity and optimum cut-off points of the prognostic scoring tools analysed.

Figure 1



Highlights

- Mortality for patients admitted to a general ICU, with a background of liver cirrhosis, maybe lower than previously reported in the literature;
- Lactate and ascites were independent predictors of ICU mortality in this cohort of patients;
- The simple addition of serum lactate levels into the Child- Turcotte-Pugh score may provide a clinically useful scoring tool for critical care clinicians.