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The LIVERAID (LIVER And Infectious Diseases)-ICU score predicts in-hospital mortality in liver cirrhosis patients with infections in the intensive care unit

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ABSTRACT

Objectives The admission of patients with liver cirrhosis to the intensive care unit (ICU) due to infections is a frequent occurrence, often leading to complications such as hepatic encephalopathy, renal failure and circulatory collapse, significantly elevating mortality risks. Accurate and timely diagnosis and intervention are critical for improving therapeutic outcomes. In this context, medical scoring systems in ICUs are essential for precise diagnosis, severity assessment and appropriate therapeutic strategies. There are no specific models for the prediction of mortality in ICU patients with liver cirrhosis-associated infections. This study aims to develop an improved prognostic scoring system for predicting in-hospital mortality among liver cirrhosis patients with infections in the ICU. This scoring system is designed to enhance the predictive accuracy of in-hospital mortality complementing existing sepsis and liver-specific prognostic models.

Methods A retrospective analysis was conducted in 620 patients with liver cirrhosis, treated for infections in the ICU of a German university hospital during 2017–19. Advanced statistical techniques were employed to develop and validate the LIVERAID (LIVER And Infectious Diseases)-ICU score, a novel scoring system specifically tailored for liver cirrhosis patients in the ICU with infections. The development of the multivariable logistic regression model involved selecting variables with the highest prognostic efficacy, and its predictive performance was assessed using calibration plots and the concordance statistic (c-index) to evaluate both calibration and discrimination.

Results The LIVERAID-ICU score integrates Child-Pugh class, serum urea levels and respiratory metrics. It is designed for bedside calculation using basic clinical and laboratory data, with no need for additional tools. In the validation cohort, the LIVERAID-ICU score exhibited enhanced sensitivity and specificity (AUC=0.83) in forecasting in-hospital mortality of patients with liver cirrhosis-associated infections when compared with established scores like Sequential Organ Failure Assessment (SOFA) (p=0.045), Model for End-Stage Liver Disease (MELD) (p=0.097), Child (p<0.001) and CLIF consortium acute-on-chronic liver failure (CLIF-C ACLF) (p<0.001).

Conclusion The newly developed LIVERAID-ICU score represents a robust, streamlined and easy tool for predicting in-hospital mortality in liver cirrhosis patients with infections, surpassing the predictive capabilities of established liver or sepsis scores like SOFA, MELD, Child and CLIF-C ACLF. The reliance of the LIVERAID-ICU score on fundamental clinical and laboratory data facilitates its global application in ICUs, enabling immediate application at the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with liver cirrhosis are frequently admitted to the intensive care unit (ICU) due to infections. Existing prediction models like Sequential Organ Failure Assessment (SOFA), quick SOFA (qSOFA), Child-Pugh, Model for End-Stage Liver Disease (MELD) and CLIF consortium acute-on-chronic liver failure (CLIF-C ACLF) score lack specificity and accuracy for predicting mortality in these patients.

WHAT THIS STUDY ADDS

⇒ This study introduces the LIVERAID (LIVER And Infectious Diseases)-ICU score, a novel prognostic tool specifically designed to predict in-hospital mortality for ICU patients with liver cirrhosis-related infections, demonstrating superior predictive accuracy over established sepsis and liver scores. The LIVERAID-ICU score was developed and validated using two well-characterised and independent cohorts and integrates Child-Pugh class, serum urea levels and respiratory metrics and can be calculated bedside without using additional tools.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The new LIVERAID-ICU score is designed for easy application and offers superior predictive accuracy for in-hospital mortality of patients with liver cirrhosis-associated infections compared with existing models such as SOFA, qSOFA, Child-Pugh, MELD and CLIF-C ACLF. Its implementation has the potential to significantly enhance clinical management of ICU patients with liver cirrhosis and infections. By enabling more effective therapeutic interventions, it could also contribute to reducing in-hospital mortality rates.

bedside for patients with liver cirrhosis during episodes of suspected or confirmed infections.

INTRODUCTION

Patients with liver cirrhosis frequently experience infections, which significantly influence their outcomes.[1–3] It is estimated that between 25% and 35% of all patients admitted to the hospital for decompensated liver cirrhosis present with an infection at the time of admission or acquire an infection during their hospitalisation.[4–7] These infections commonly precipitate complications such as circulatory shock, hepatic encephalopathy or renal failure, causing elevated mortality rates.[8 9]

Liver cirrhosis exacerbates infection-related consequences by compromising immune system function. This phenomenon is summarised in the concept of cirrhosis-associated immune dysfunction (CAID), which is characterised by two primary mechanisms: a persistent immunodeficiency impacting both the innate and adaptive immune systems and a dysregulated activation of the immune system resulting in the overproduction of inflammatory cytokines.[10 11] This apparent dichotomy in immune system function increases susceptibility to infections due to immunodeficiency. Concurrently, these infections provoke an overactive immune response, culminating in the onset of shock states and subsequent organ failure leading to acute-on-chronic liver failure (ACLF).[12–14] ACLF is a distinct syndrome that develops in patients with acute decompensation of cirrhosis, characterised by multiorgan failure and a high short-term mortality and is mainly triggered by infections.[8 15] Sepsis is the cause of ACLF in 30% of cases.[16 17]

Consequently, the prompt recognition and immediate treatment of infections in patients with liver cirrhosis are imperative. Diagnosing infections in these patients can be particularly challenging due to the atypical presentation of symptoms as a consequence of CAID. Commonly, patients with liver cirrhosis do only show limited clinical infection indicators such as fever or leucocytosis, and the levels of C reactive protein and procalcitonin are typically only moderately elevated. Additionally, these patients frequently lack specific symptoms, especially in pneumonia and urinary tract infections. Studies have demonstrated an inverse relationship between the severity of liver disease and the clinical manifestations of infections.[18] Often, the onset of hepatic encephalopathy or a decline in hepatic or renal function is the primary indicator of an underlying infection.[19]

There is no score specially designed for patients with liver cirrhosis-associated infections. Established prediction models like Sequential Organ Failure Assessment (SOFA) score,[20] quick SOFA (qSOFA) score,[21] Child-Pugh score (CP score),[22 23] Model for End-Stage Liver Disease (MELD)[24–26] and CLIF-C ACLF (acute-on-chronic liver failure) have a low accuracy for the prediction of mortality in patients with liver cirrhosis and infections.[27] Access to enhanced predictive tools for prognosis remains an unresolved challenge. Advancements in these domains hold the potential to facilitate earlier interventions, thereby preventing the onset of complications.[28]

Thus, formulating innovative, sensitive and straightforward methodologies for the early prediction of prognosis in patients with liver cirrhosis and infections emerges as a critical imperative to facilitate the initiation of timely therapeutic interventions.[20 29] Therefore, the objective of this study was to develop and validate a novel scoring system, designated as the LIVERAID (LIVER And Infectious Diseases)-ICU score. This score is designed to precisely predict in-hospital mortality of patients with liver cirrhosis-associated infections, enhancing clinical outcomes and patient care in critical care settings.

METHODS

Study design and patient cohort

This retrospective, single-centre study was conducted at the intensive care unit (ICU) of the Department of Internal Medicine I at the University Hospital Regensburg, Regensburg, Germany. Adherence to ethical standards was ensured by conducting the study in alignment with the Declaration of Helsinki, and it received approval from the Institutional Review Board of the University Hospital Regensburg (approval code: 19-1528-104). All patients were identified directly from patient charts. Patient data were extracted from in-hospital documentation systems, patient monitoring programmes and individual patient files. All laboratory tests were conducted at the Institute of Clinical Chemistry and Laboratory Medicine at the University Hospital Regensburg, Regensburg, Germany. The collection of vital and laboratory parameters for score calculation was specifically undertaken on the diagnosis of an infection, as we aimed to develop a new score predicting the prognosis of patients with liver cirrhosis and infections at the earliest possible time, that is, at the time of the diagnosis of an infection. To avoid overfitting, mechanical ventilation was only recorded before liver transplantation.

A cohort of 620 patients diagnosed with liver cirrhosis and infections as primary clinical issues admitted to the ICU over a period of 3 years between January 2017 and December 2019 was identified for the study. The ICU is highly specialised in patients with liver diseases with a wide catchment area. The diagnosis of liver cirrhosis was based on current guidelines.[30] Criteria for inclusion encompassed the presence of a diagnosed infection. Infections in patients with liver cirrhosis in the ICU were diagnosed by specialists for internal medicine, gastroenterology and hepatology, infectious diseases and intensive care medicine, certified by the Bavarian Board of Doctors, based on clinical examination, laboratory and microbiological tests, and medical imaging in accordance with The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), and EASL Clinical Practice Guidelines on ACLF.[20 31] Furthermore, only patients with liver cirrhosis were included, for whom infection was noted in the primary diagnoses of the final medical letter from the ICU.

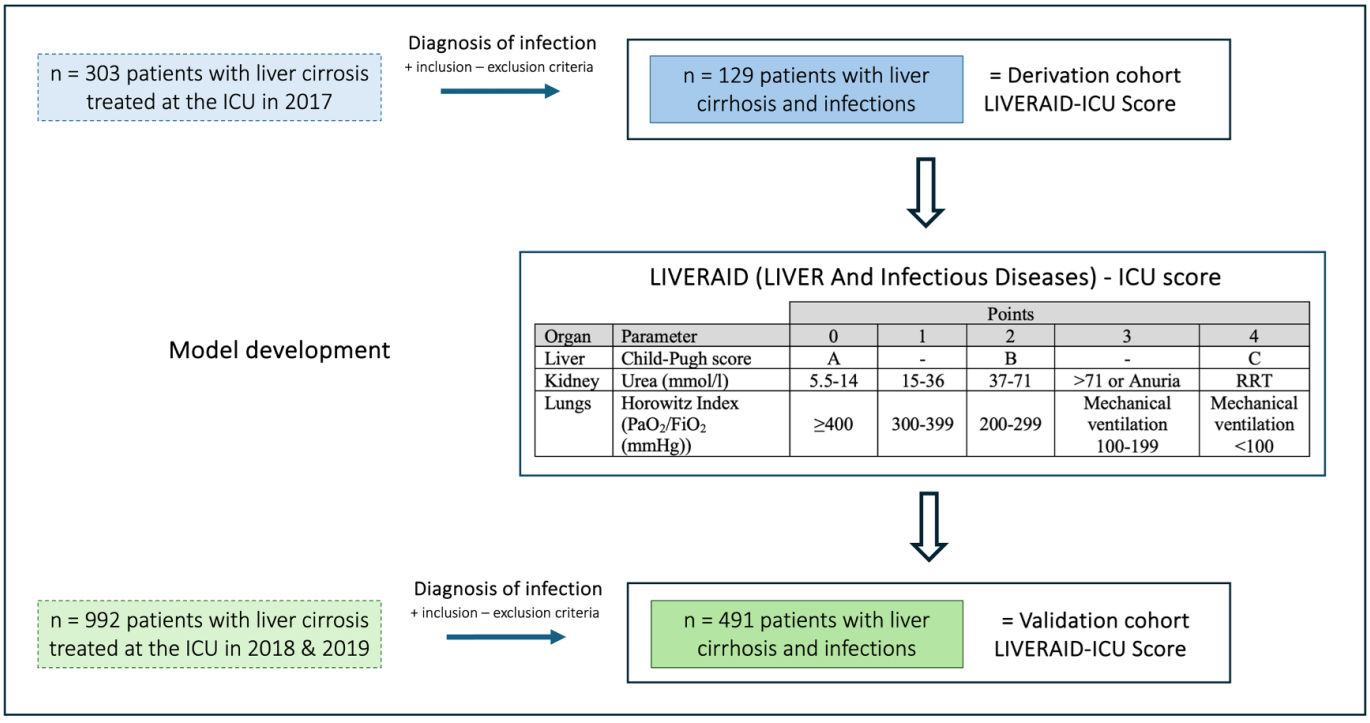

Figure 1 Flow chart of the patient selection process for the derivation and validation cohort of the LIVERAID-ICU score. 303 patients with liver cirrhosis treated at the ICU in 2017 were screened for infections as the primary clinical issue. Applying inclusion and exclusion criteria, 129 patients were identified for the derivation cohort. The score was validated in a cohort of 491 patients with liver cirrhosis and infections as the primary clinical issue treated in the ICU in 2018 and 2019. Screening of 992 patients with liver cirrhosis was performed to identify these patients. ICU, intensive care unit.

Exclusion criteria comprising patients under 18 years of age, those with a history of liver transplantation and patients with liver cirrhosis hospitalised at the ICU due to another primary clinical issue such as GI-Bleeding, acute intoxication, alcohol-induced decompensation and pancreatitis, or post-operative and post-interventional monitoring. The primary outcome measured in this study was in-hospital mortality. Data analysis for developing the novel score was performed using information from 129 patients admitted to the ICU in 2017, while validation of the score used data from 491 patients admitted between 2018 and 2019. Flow charts of the patient selection process for the derivation and validation cohort are shown in figure 1.

Score calculation and validation

For comparative purposes, scores were calculated using established methods, including the SOFA score,[20] qSOFA score,[21] CP score,[22 23] MELD[24–26] and CLIF-C ACLF (acute-on-chronic liver failure) score, as defined in the literature.[32] The specific point of time for these calculations corresponded with the diagnosis of an infection. In patients who did not have an arterial blood gas analysis, the SpO2/FiO2 ratio was used to determine the PaO2/FiO2 ratio. Valid methods were used for calculation.[33 34]

Statistical analysis

Descriptive statistics were used to summarise the dataset characteristics. Continuous variables were expressed either as mean±SD or as median with IQR, contingent on the distribution properties of the data. Categorical variables were delineated through both absolute and relative frequencies. The relationship between in-hospital mortality and various clinical parameters was studied using univariate logistic regression models. The construction of the novel prognostic score for predicting in-hospital mortality is reported in alignment with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement (online supplemental file 1).[35]

Model development

The construction of the multivariable logistic regression model involved the selection of variables exhibiting the utmost prognostic efficacy. The model employed ORs and 95% CIs as measures of effect size. Predictor variables within the model were stratified into five distinct categories, paralleling the SOFA score's structure, with scores ranging from 0 to 4. This categorisation process was informed by a synthesis of clinical acumen, statistical demarcations and insights gleaned from other assessment tools. The cumulative sum of all category scores constituted the final prognostic score.

Model validation

The predictive capability of the developed score was appraised through calibration plots and the concordance statistic (c-index), thereby evaluating both the calibration and discrimination aspects of the model. Internal validation was accomplished via a bootstrap validation (n=1000 replications) to derive optimism-corrected estimates. An

external validation process was executed, encompassing a cohort of 491 patients diagnosed with liver cirrhosis-associated infections, admitted to the ICU during 2018 and 2019.

Statistical significance was established at a p value threshold of <0.05. All statistical analyses were conducted using R software, V.3.5.5 (The R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

This study was conducted to improve the future care of ICU patients with liver cirrhosis and infections by developing a new prognostic score. The LIVERAID-ICU score was designed with the aim of addressing the urgent need for more accurate prognoses and better treatment decisions in the ICU. The results of this study will be also shared at dedicated events for patients and their families. Collaboration with patient organisations will help to ensure that the findings are accessible and useful to those affected.

RESULTS

Demographic and clinical characteristics of the study population

The initial phase of this study involved a detailed analysis of a cohort comprising 129 patients with liver cirrhosis, identified between January and December 2017, who met the specified inclusion criteria. This analysis was integral to the development of the novel LIVERAID-ICU score. The mortality rate within this cohort was 37.2%, with 48 patients dying from their conditions; notably, 87.5% of these mortalities occurred within the ICU setting.

A comprehensive evaluation of the aetiologies of liver cirrhosis in these patients revealed that the predominant cause was alcohol-related liver disease, accounting for 53.3% of cases, followed by viral hepatitis, which was identified in 7.3% of the patients. The albumin was significantly reduced with 21.00 (q1 17.60, q4 26.00) g/L. The marked reduction in albumin reflects the severity of the liver disease. The median duration of ICU hospitalisation was 7 days, with a range extending from 4 to 20 days and a maximum hospitalisation period of 55 days. ACLF, as defined in the literature,[31] was diagnosed in 66.7% (n=86) of the patients. Liver transplantation was performed in seven patients subsequent to sepsis treatment.

The primary sources of infections were identified as pneumonia (n=42, 32.58%), urinary tract infection (n=35, 27.13%)), spontaneous bacterial peritonitis (n=29, 22.48%), cholangiosepsis (n=18, 13.95%) and soft-tissue infections (n=5, 3.88%). Successful microbiological detection was achieved in 75.2% (n=97) of the cases. Comprehensive demographic and clinical characteristics of the study population are outlined in table 1.

Identification of predictors of in-hospital mortality

To develop the new prognostic score, independent predictors of in-hospital mortality were systematically identified among patients with liver cirrhosis and infections.

Table 1 Characteristics of patients (n=129) included in the analyses for the development of the novel LIVERAID-ICU score

Patient characteristics	Statistical data and measurements
Age (year)	58.2 (SD 10.5)
Male	83 (64%)
BMI (kg/m²)	26.3 (SD 5.6)
In-hospital mortality	48 (37.2%)
Time to death (days)	17.5 (SD 12.61)
Liver transplantation	9 (7.0%)
Time to transplantation	11.22 (SD 8.74)
Reason for hospitalisation at the ICU	
Hepatic encephalopathy	69 (53.49%)
Respiratory insufficiency	42 (32.56%)
Circulatory insufficiency	18 (13.95%)
Requirement of organ support	
Renal replacement therapy	49 (37.98%)
Mechanical ventilation	38 (29.46%)
Need for vasopressors	45 (34.88%)
Heart rate (/min)	89.62 (SD 18.01)
Blood pressure (sys.)	105.74 (SD 18.64)
Lowest MAP in the first hour	72.24 (SD 12.36)
Respiratory rate (per min)	19.39 (SD 4.71)
PaO_2/FiO_2	318.42 (SD 112)
Albumin (g/L)	21.00 (q1 17.60, q3 26.00)
Bilirubin (mg/dL)	4.7 (q1 1.60, q3 13.60)
Creatinine (mg/dL)	1.53 (q1 0.91, q3 2.37)
C reactive protein (mg/L)	36.00 (q1 17.20, q3 80.00)
GFR (mL/min/1.73 m²; CKD-EPI)	45.00 (q1 26.00, q3 86.00)
Highest lactate in the first hour (mmol/L)	1.9 (q1 1.20, q3 3.66)
Na (mmol/L)	138.00 (q1 132.00, q3 142.00)
Platelet count (per nL)	89.00 (q1 50.00, q3 146.00)
Procalcitonin (g/mL)	0.90 (q1 0.36, q3 3.12)
Prothrombin time (%)	43.00 (q1 32.00, q3 45.00)
Urea (mmol/L)	78.00 (q1 49.00, q3 117.00)
Pre-existing TIPS	33 (26%)
CP count	10.72 (SD 1.75)
CP class	
Child A	0 (0%)
Child B	34 (26%)
Child C	95 (74%)
MELD score	24.61 (SD 9.31)
ACLF	86 (67%)

Continued

Table 1 Continued

Patient characteristics	Statistical data and measurements
CLIF-C ACLF score	57.10 (SD 9.50)
ACLF grade	2.2 (SD 0.8)
SOFA	9.07 (SD 4.01)
qSOFA	1.7 (SD 0.95)
Septic shock	25 (19%)
SAPS II	22 (SD 10.49)

ACLF, acute-on-chronic liver failure; BMI, Body Mass Index; CKD-EPI, chronic kidney disease epidemiology; CLIF-C ACLF, CLIF consortium acute-on-chronic liver failure; CP, Child-Pugh; GFR, glomerular filtration rate; ICU, intensive care unit; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; qSOFA, quick SOFA; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; TIPS, transjugular intrahepatic portosystemic shunt.

Key among these independent prognostic indicators was the incidence of septic shock, which manifested significantly more frequently in non-surviving patients compared with survivors (64% vs 36%, OR 4.00, p=0.003). The CP score also emerged as a significant factor, with survivors having a mean CP score of 10.28 (SD 1.76) vs 11.46 (SD 1.49) in non-survivors (OR 1.53, p<0.001). Similarly, stratification by CP stage revealed a marked difference in survival outcomes (stage B: 91% survival vs 9% mortality; stage C: 53% survival vs 47% mortality, OR 9.3, p<0.001). Additionally, levels of bilirubin (survivors: mean 6.87 (SD 9.18) vs non-survivors: mean 12.91 (SD 11.14), OR 1.06, p=0.002) and the MELD score (survivors: mean 21.62 (SD 8.59) vs non-survivors: mean 29.67 (SD 8.3), OR 1.11, p<0.001) were significantly correlated with overall survival.

In summary, univariate logistic regression models were used to identify predictors of in-hospital mortality; refer to table 2 for an overview of these findings.

Development of the LIVERAID-ICU score

Subsequent to the identification of significant variables through univariate regression analyses, as detailed in tables 1 and 2, comprehensive multivariate regression analysis was undertaken. This phase entailed a preliminary variable selection using forward selection methodologies. The resultant multivariate model, integrating three distinct parameters, was found to most accurately predict in-hospital mortality in the patient cohort with liver cirrhosis and infections. The results of this multivariate analysis, summarising the definitive prognostic factors, are presented in table 3.

Establishment of the LIVERAID-ICU score utilizing identified prognostic parameters to assess outcomes in ICU patients with liver cirrhosis-related infections

Following the identification of the three essential prognostic parameters—the Child-Pugh score, urea levels and the Horowitz Index—a systematic approach was employed to subdivide each parameter into quintiles, analogous to the methodology used in the SOFA score. Specifically, the Child-Pugh score was discretised in alignment with its conventional three-class system. The stratification of urea levels incorporated a multifaceted criterion, including laboratory benchmarks (spanning normal to severe deviations), daily urinary output and the necessity of renal replacement therapy (RRT). Patients undergoing RRT are stratified with four points (= max.) in the kidney section of the LIVERAID-ICU score. The Horowitz Index was integrated as defined within the SOFA score, categorised into five distinct subscales.

The synthesis of these analytical processes led to the establishment of the novel LIVERAID-ICU score, specifically tailored for patients admitted to the ICU with liver cirrhosis-related infections. This scoring system, detailed in table 4, is structured to range from a minimum of 0 to a maximum of 12 points, thereby providing a comprehensive assessment tool for prognostication of in-hospital mortality of patients with liver cirrhosis-related infections.

Diagnostic performance of the LIVERAID-ICU score in the derivation cohort

In the derivation cohort, the c-index (AUC) for predicting in-hospital mortality was high, with a c-index of 0.89. Somers' D_{xy} rank correlation between the predicted probabilities and the observed responses was 0.771, indicating robust predictive accuracy.

Validation of the LIVERAID-ICU score

To substantiate the efficacy of the LIVERAID-ICU score, a series of validation methodologies were employed:

Bootstrap validation of the LIVERAID-ICU score for internal consistency

An internal validation of the LIVERAID-ICU score was conducted to acquire stable, optimism-corrected estimates. This was achieved through bootstrap validation with n=1000 repetitions. The resulting optimism-corrected c-index stood at 0.88, while the adjusted D_{xy} was 0.767, affirming the model's internal consistency.

Calibration plot analysis of the LIVERAID-ICU score

A detailed calibration plot, illustrating the alignment between predicted and actual probabilities, is presented in figure 2A. This plot compares apparent and bias-corrected probabilities to the ideal reference line, demonstrating the commendable overall calibration of the LIVERAID-ICU score.

Evaluation of the discrimination capability of the LIVERAID-ICU score

Comparative analyses underscored the superior discriminatory ability of the LIVERAID-ICU score, particularly in predicting in-hospital mortality among liver cirrhosis patients in the ICU with suspected infection or sepsis.

Table 2 Univariable logistic regression models for the identification of predictors of in-hospital mortality of patients with liver cirrhosis and infections. For each parameter, numbers of survivors and non-survivors OR and p value are shown

Parameter	Survivors (n=81)	Non-survivors (n=48)	OR (95% CI)	P value
Heart rate (n=129)	88.19 (SD 16.78)	92.04 (SD 19.86)	1.01 (0.99, 1.03)	0.240
Blood pressure (sys) (n=129)	107.19 (SD 17.25)	103.29 (SD 20.74)	0.99 (0.97, 1.01)	0.252
Lowest MAP in the first hour (n=129)	73.7 (SD 12.24)	69.77 (SD 12.28)	0.97 (0.94, 1)	0.083
Respiratory rate (n=101)	18.95 (SD 4.34)	20.17 (SD 5.3)	1.06 (0.97, 1.16)	0.216
Horowitz Index	351.76 (SD 103.49)	262.15 (SD 103.83)	0.99 (0.99, 1)	<0.001
Albumin (n=129)	22.11 (SD 6)	22.55 (SD 6.88)	1.01 (0.95, 1.07)	0.705
Bilirubin (n=129)	6.87 (SD 9.18)	12.91 (SD 11.14)	1.06 (1.02, 1.1)	0.002
Creatinine	1.72 (SD 1.22)	2.07 (SD 1.21)	1.26 (0.94, 1.72)	0.119
C reactive protein (n=129)	57.65 (SD 64.65)	54.49 (SD 43.56)	1 (0.99, 1.01)	0.763
GFR (n=109)	57.5 (SD 33.29)	43.73 (SD 26.58)	0.99 (0.97, 1)	0.035
Highest lactate in the first hour (n=129)	2.37 (SD 1.97)	3.8 (SD 3.6)	1.22 (1.06, 1.44)	0.010
Na (n=129)	137.32 (SD 7.9)	136.04 (SD 8.47)	0.98 (0.94, 1.02)	0.386
Platelet count (n=129)	140.26 (SD 160.96)	83.9 (SD 68.13)	0.99 (0.99, 1)	0.015
Procalcitonin (n=129)	6.4 (SD 20.91)	6.31 (SD 20.59)	1 (0.98, 1.02)	0.981
Prothrombin time (n=129)	47.05 (SD 19.12)	37.54 (SD 18.34)	0.97 (0.95, 0.99)	0.009
Urea (n=129)	77.1 (SD 44.99)	113.81 (SD 62.02)	1.01 (1.01, 1.02)	<0.001
CP count (n=129)	10.28 (SD 1.76)	11.46 (SD 1.49)	1.53 (1.22, 1.97)	<0.001
TIPS (n=125)				
No TIPS	51 (55%)	41 (45%)		
TIPS	26 (79%)	7 (21%)	0.33 (0.12, 0.81)	0.021
CP class (n=129)				
Child A	0 (0%)	0 (0%)		
Child B	31 (91%)	3 (9%)		
Child C	50 (53%)	45 (47%)	9.3 (3.05, 40.6)	0.000
MELD score (n=129)	21.62 (SD 8.59)	29.67 (SD 8.3)	1.11 (1.06, 1.17)	<0.001
SOFA (n=129)	7.51 (SD 3.19)	11.71 (SD 3.9)	1.38 (1.23, 1.58)	<0.001
SOFA cardiovascular	1.17 (SD 1.43)	1.94 (SD 1.64)	1.38 (1.09, 1.75)	0.008
SOFA CNS	0.75 (SD 1.04)	1 (SD 1.01)	1.25 (0.89, 1.79)	0.195
SOFA coagulation	1.4 (SD 1.09)	2.04 (SD 1.27)	1.61 (1.18, 2.25)	0.004
SOFA liver	1.91 (SD 1.36)	2.90 (SD 1.13)	1.81 (1.33, 2.46)	<0.001
SOFA renal	1.02 (SD 1.13)	1.85 (SD 1.38)	1.68 (1.26, 2.31)	0.001
SOFA respiration	1.25 (SD 1.19)	1.98 (SD 1.06)	1.73 (1.26, 2.42)	0.001
qSOFA (n=129)	1.46 (SD 0.95)	2.1 (SD 0.81)	2.23 (1.47, 3.52)	<0.001
Septic shock (n=129)				
No	72 (69%)	32 (31%)		
Yes	9 (36%)	16 (64%)	4 (1.63, 10.37)	0.003

CNS, central nervous system; CP, Child-Pugh; GFR, glomerular filtration rate; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; qSOFA, quick SOFA; SOFA, Sequential Organ Failure Assessment; TIPS, transjugular intrahepatic portosystemic shunt.

This enhanced discriminatory capacity, when compared with other established scores such as SOFA, qSOFA, Child-Pugh, MELD and CLIF-C ACLF, is graphically represented in figure 2B. Notably, the LIVERAID-ICU score exhibited superior sensitivity and specificity, as shown by its significantly higher area under the curve (AUC) values. This score is advantageous because it specifically focuses on infections related to liver cirrhosis, unlike existing scores which have a more generalised approach that is, either on sepsis or liver failure.Comparative analyses underscored the superior disc.

Diagnostic performance of the LIVERAID-ICU score in the validation cohort

The robustness of the LIVERAID-ICU score was further evaluated through external validation in an independent

Table 3 Multivariable logistic regression model for the prediction of in-hospital mortality of patients with liver cirrhosis and infections. The three parameters found to be best predicting in-hospital mortality with OR and p value are presented

Parameter	OR (95% CI)	P value
Child-Pugh score	1.62 (1.22, 2.14)	0.001
Urea (per 10 mmol/L)	1.13 (1.04, 1.24)	<0.001
Horowitz Index (PaO_2/FiO_2) (per 10 mm Hg)	0.91 (0.87, 0.95)	0.004

cohort, encompassing 498 liver cirrhosis patients hospitalised from January 2018 to December 2019. Baseline characteristics of this cohort are delineated in table 5. The AUC of the LIVERAID-ICU score for predicting in-hospital mortality was 0.83. Furthermore, our analyses showed an excellent discriminatory ability of the LIVERAID-ICU score compared with other scores concerning the in-hospital mortality of patients with cirrhosis-related infections admitted to the ICU. The discriminatory ability of the LIVERAID-ICU score in comparison to the SOFA (p=0.045), qSOFA (p<0.001), Child score (p<0.001), MELD score (p=0.097) and CLIF-C ACLF (p<0.001) is depicted in figure 3A and B.

In summary, the new LIVERAID-ICU score emerges as a prognostic tool, specifically designed for the evaluation of patients with pre-existing liver cirrhosis with a suspected infection in the ICU. This scoring system demonstrates superior accuracy efficacy over established sepsis and liver scores in patients with liver cirrhosis-related infections.

DISCUSSION

In patients with liver cirrhosis, infection onset often correlates with a poorer prognosis, as suggested by existing literature.[36–42] The rising global incidence of liver cirrhosis and liver cirrhosis-related infections has increased the admission rate of these patients to ICUs worldwide.[43] This global trend underscores the need for a specialised prognostic tool tailored to predict the clinical outcomes of patient with liver cirrhosis-associated infections, particularly at the critical interface of suspected infection and the initiation of intensive care management.[28] Current evidence suggests an absence of a specific scoring system explicitly designed for the assessment of patients with liver cirrhosis undergoing treatment for infection, revealing a significant gap in the clinical management framework of this vulnerable patient cohort.

Despite advancements in defining sepsis, the application of existing scoring systems for outcome prediction in patients with chronic organ dysfunction remains a clinical challenge. The SOFA score, for instance, lacks validation for patients with chronic conditions.[20] This is particularly pertinent as chronic diseases variably influence the onset and progression of sepsis. Liver cirrhosis, for example, significantly impacts hepatic function, coagulation and the central nervous system.[3] These cirrhosis-induced hepatic and systemic alterations, which manifest in clinical changes of both vital signs and laboratory parameters, necessitate their integration into any effective scoring system designed for patients with liver cirrhosis-associated infections. Such inclusion is essential for accurately assessing the impact of chronic organ dysfunction and infection on patient outcomes.

The application of the SOFA score criteria for sepsis[20 44 45] is recommended for establishing baseline values in patients with sepsis. However, as evidenced in our study, these baseline values are often not readily available at the time of a patient's admission to an ICU. This lack of immediate access to baseline data likely impairs the discriminatory capability of the SOFA score. Despite this limitation, the SOFA score has demonstrated commendable efficacy in predicting in-hospital mortality, suggesting its utility even in the absence of initial baseline measurements. This finding underscores the potential of the SOFA score as a valuable prognostic tool in the ICU setting, although with considerations for its limitations in immediate data availability.

Our research introduces the LIVERAID-ICU score, a novel prognostic tool that demonstrably surpasses the SOFA score in predicting outcomes for ICU patients with liver cirrhosis-related infections, as substantiated by a statistically significant difference (p=0.016, refer

Table 4 LIVERAID-ICU score. Parameters representing the function of the liver, kidneys and lungs and division into five subscales

		Points				
Organ	Parameter	0	1	2	3	4
Liver	Child-Pugh score	A	–	B	–	C
Kidney	Urea (mmol/L)	5.5–14**	15–36	37–71	>71 or anuria†	RRT‡
Lungs	Horowitz Index (PaO_2*/FiO_2 (mm Hg))	≥400	300–399	200–299	Mechanical ventilation 100–199	Mechanical ventilation <100

*Instead of PaO_2, SpO_2 can also be used.[29 30]
†<500 mL/day.
‡Any type of RRT, even one time.
RRT, renal replacement therapy.

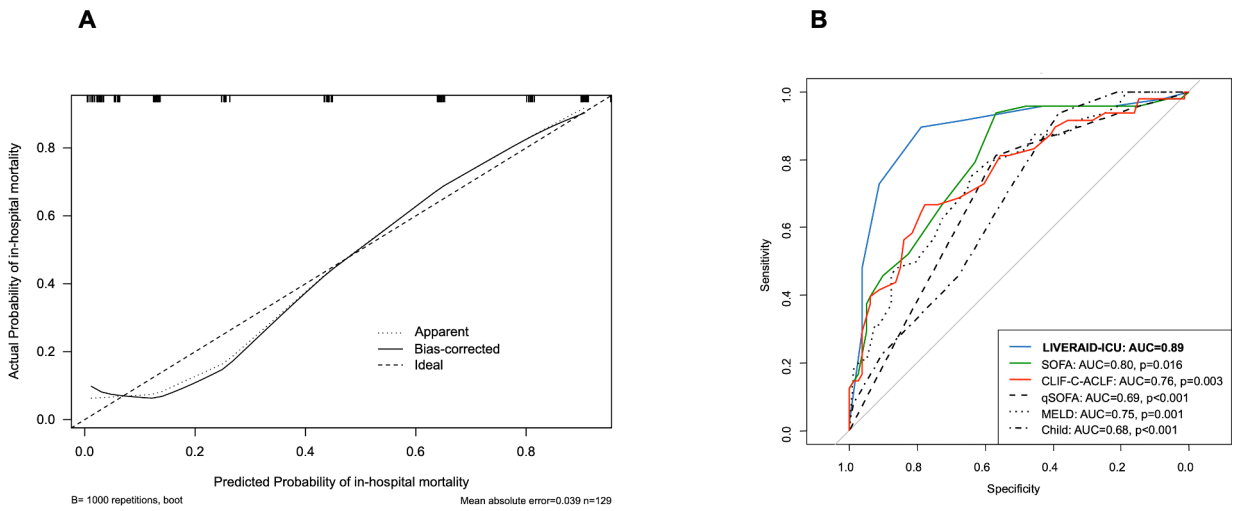

Figure 2 (**A**) Calibration plot showing the LIVERAID-ICU score predicting in-hospital mortality probabilities compared with the true mortality probabilities. (**B**) ROC comparing the prediction of in-hospital mortality by different scores. AUC values and p values comparing established scores with the LIVERAID-ICU score are provided in the legend. ICU, intensive care unit; AUC, area under the curve; ROC, receiver operating characteristic.

to figure 2B). In addition to complementing the SOFA score, which is primarily tailored for sepsis patients, the LIVERAID-ICU score also shows superior predictive accuracy for in-hospital mortality compared with established liver-specific scoring systems. While scores such as the Child-Pugh and MELD are adept at predicting outcomes for patients with liver cirrhosis, their predictive power diminishes at the interface of liver cirrhosis and infections.

It is widely recognised that ICU-specific scores, like the SOFA and qSOFA, more effectively predict patient outcomes in the ICU setting than liver-specific scores. This assertion is corroborated by our study. Notably, the LIVERAID-ICU score significantly outperforms these liver-specific scores in predicting patient outcomes, with its AUC being markedly higher (LIVERAID-ICU AUC=0.89) compared with both MELD (AUC=0.75, p=0.001) and Child-Pugh scores (AUC=0.68, p<0.001). This enhanced predictive accuracy of the LIVERAID-ICU score emphasises its potential as a more effective tool for assessing prognosis in patients with chronic liver disease and infections admitted to the ICU.

The CLIF-C ACLF score, developed from the data of the CANONIC study, is a prognostic tool specifically designed for ACLF. It surpasses both the MELD (Model for End-Stage Liver Disease) score and the Child-Pugh score in predicting the prognosis of ACLF.[32 46] ACLF often, though not invariably, arises following an infection. However, it is crucial to note that not all patients with infections progress to ACLF. In our study, 66.7% of the patients met the criteria for ACLF according to the EASL-CLIF definition.[15]

The LIVERAID-ICU score significantly outperformed CLIF-C ACLF score (p=0.003) in our study population of patients with liver cirrhosis, treated for infections in the ICU. In contrast to the CLIF-C ACLF score, the LIVERAID-ICU score is designed to predict prognosis across all patients with liver cirrhosis-related infections on the ICU, not just those with ACLF. Importantly, the LIVERAID-ICU score is the first and only tool specifically developed specifically for patients with liver cirrhosis-associated infections.

In the field of critical care medicine, the introduction of a new scoring system necessitates not just parity with established scores but a demonstrable enhancement of the field. This enhancement is mainly achieved by improved prediction accuracy, as seen in increased sensitivity and specificity metrics. Given the high mortality rates in the patient cohort under investigation, it is imperative for a new score to achieve robust sensitivity without compromising specificity. The LIVERAID-ICU score clearly fulfils these criteria.

Equally important is the practical usability of the new score in terms of collecting parameters quickly and cost-effectively. The LIVERAID-ICU score excels in this aspect by relying exclusively on parameters that are routinely assessed on admission to the ICU.

Another notable advantage of the LIVERAID-ICU score is its simplicity in calculation. Unlike some scoring systems that require complex algorithms or specialised software for computation, the LIVERAID-ICU score can be determined through a straightforward summation of point parameters. The ease of calculation improves its usefulness in fast-paced clinical settings such as an ICU.

Furthermore, the implementation of the LIVERAID-ICU score does not impose any additional burden on clinical staff, particularly in the context of calculating the Child-Pugh score, which is already a routine assessment for patients with liver cirrhosis. Thus, the LIVERAID-ICU score stands out not only for its predictive accuracy but also for its practicality and ease of integration into existing clinical workflows.

The data supporting our study were collected retrospectively as part of a single-centre investigation. A

Table 5 Characteristics of the patients (n=491) included in the validation cohort

Patient characteristics	Statistical data and measurements
Age (year)	58.1 (SD 10.71)
Male	344 (70.1%)
BMI (kg/m²)	26.67 (SD 6.30)
In-hospital mortality	144 (29.33%)
Time to death	14.6 (SD 11.32)
Liver transplantation	23 (4.68%)
Time to transplantation	9.41 (SD 6.18)
Reason for hospitalisation at the ICU	
Hepatic encephalopathy	251 (51.12%)
Respiratory insufficiency	161 (32.80%)
Circulatory insufficiency	79 (16.09%)
Requirement of organ support	
Renal replacement therapy	161 (32.79%)
Mechanical ventilation	135 (27.49%)
Need for vasopressors	160 (32.59%)
Heart rate (/min)	87.58 (SD 18.85)
Blood pressure (sys.)	109.29 (SD 22.51)
Lowest MAP in the first hour	76.10 (SD 15.92)
Respiratory rate (per min)	18.35 (SD 5.60)
PaO_2/FiO_2	353.77 (SD 114.71)
Albumin (g/L)	24.00 (q1 20.00, q3 29.35)
Bilirubin (mg/dL)	4.9 (q1 2.10, q3 12.70)
Creatinine (mg/dL)	1.58 (q1 0.98, q3 2.65)
C reactive protein (mg/L)	31.10 (q1 12.90, q3 68.30)
GFR (mL/min/1.73 m²; CKD-EPI)	46.00 (q1 24.00, q3 76.00)
Highest lactate in the first hour (mmol/L)	1.89 (q1 1.33, q3 2.89)
Na (mmol/L)	138.00 (q1 133.00, q3 142.00)
Platelet count (per nL)	77.00 (q1 48.00, q3 119.00)
Procalcitonin (g/mL)	0.41 (q1 0.17, q3 1.00)
Prothrombin time (%)	44.00 (q1 34.00, q3 55.00)
Urea (mmol/L)	83.00 (q1 47.00, q3 134.00)
Pre-existing TIPS	135 (27%)
CP count	10.73 (SD 2.01)
CP class	
Child A	8 (2%)
Child B	117 (24%)
Child C	366 (74%)
MELD score	25.24 (SD 9.03)
ACLF	295 (60.1%)
CLIF-C ACLF	54.1 (SD 9.40)
ACLF grade	2.1 (SD 0.82)
SOFA	8.61 (SD 4.16)
qSOFA	0.99 (SD 0.81)
Septic shock	79 (16.1%)
SAPS II	28.25 (SD 12.35)

ACLF, acute-on-chronic liver failure; BMI, Body Mass Index; CKD-EPI, chronic kidney disease epidemiology; CLIF-C ACLF, CLIF consortium acute-on-chronic liver failure; CP, Child-Pugh; GFR, glomerular filtration rate; ICU, intensive care unit; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; qSOFA, quick SOFA; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; TIPS, transjugular intrahepatic portosystemic shunt.

considerable amount of data, especially regarding vital parameters, originated from automated ICU monitoring and documentation systems. These systems operated continuously and autonomously, guaranteeing consistent and unbiased collection of essential data points. In addition to automated data collection, we integrated data from the documentation performed by medical and nursing staff. The combination of using automated systems and manual documentation enhances the reliability and robustness of the collected data.

The LIVERAID-ICU score has the great advantage that it predicts the prognosis of patients with liver cirrhosis and infections as soon as an infection is diagnosed. It is essential for patients with liver cirrhosis and infections to correctly assess the severity of the disease and the prognosis, especially when an infection is diagnosed. This is easily possible with the LIVERAID-ICU score without an additional tool. The sequential application of scores and the corresponding comparison was not part of this study. A follow-up study with the sequential use of the LIVERAID-ICU score and other scores is planned.

Importantly, the validity of the LIVERAID-ICU score was reinforced through external validation, which included a distinct cohort of 498 patients with liver cirrhosis. This validation process demonstrated the excellent discriminatory ability of the LIVERAID-ICU score. The extensive scope of this external validation, covering a significant patient cohort, serves to effectively alleviate the inherent limitations commonly encountered in retrospective single-centre studies. Thus, the LIVERAID-ICU score performed robustly in a distinct validation cohort and outperformed established sepsis and liver scores.

CONCLUSION

To conclude, the LIVERAID-ICU score represents a significant innovation in the assessment of patients with liver cirrhosis-related infections admitted to the ICU. Its design and structure allow it to outperform established sepsis and liver scores in predicting in-hospital mortality.

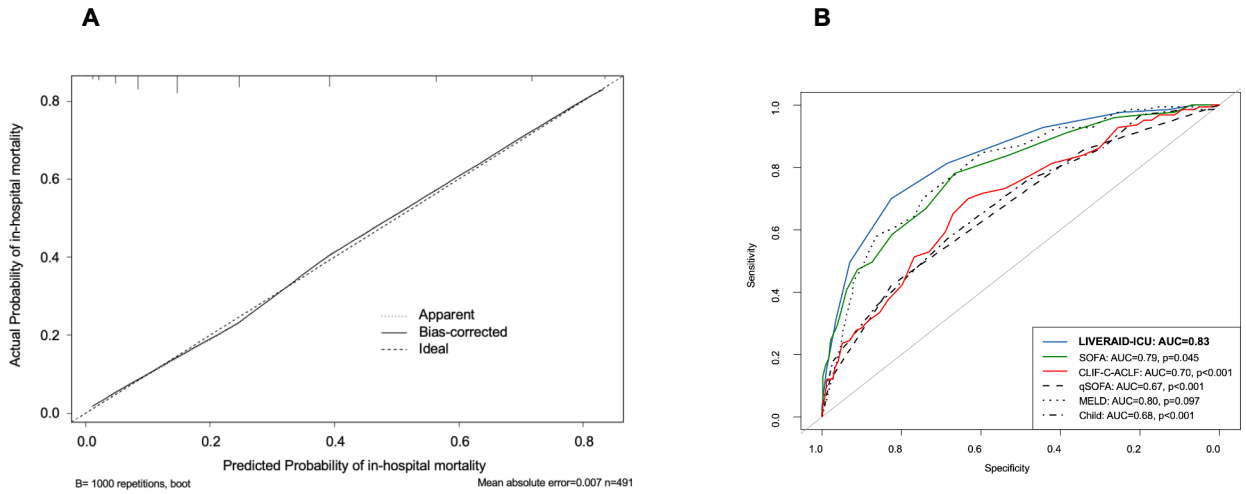

Figure 3 (**A**) Validation cohort: calibration plot showing the LIVERAID-ICU score predicting in-hospital mortality probabilities compared with the true mortality probabilities. (**B**) Validation cohort: ROC curve for the prediction of in-hospital mortality by different scores. AUC values and p values comparing established scores with the LIVERAID-ICU score are provided in the legend. ICU, intensive care unit; AUC, area under the curve; ROC, receiver operating characteristic.

The simplicity of its calculation, requiring no specialised tools, is an essential advantage. This score can be calculated at the very onset of suspected infection on admission to the ICU, making it a timely and efficient tool for clinical decision-making in emergency medicine and intensive care settings. The early applicability of the LIVERAID-ICU score, combined with its accuracy and ease of use, underscores its potential to significantly impact patient management and outcomes in the ICU, particularly in guiding early clinical interventions.

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Contributors STS is the guarantor. MM, STS and HH initiated the study. HH, FZ, DW, STS and MM analysed and interpreted the patient data. HH, STS and MM drafted the manuscript. HH and FZ performed the statistical analysis. HH, FZ, DW, PS, SOS, AM, VP, MM and STS edited the manuscript. All authors read and approved the final manuscript.

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Patient consent for publication Not applicable.

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