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A novel prognostic model to predict mortality in patients with acute-on-chronic liver failure in intensive care unit

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Abstract

Acute-on-chronic liver failure (ACLF) implies high short-term mortality rates and usually requires intensive care unit (ICU) admission. Proper prognosis for these patients is crucial for early referral for liver transplantation. The superiority of CLIF-C ACLF score in Asian patients with ACLF admitted to an ICU remains inconclusive when compared to other scoring systems. The purpose of the study is (i) to compare the predictive performance of original MELD, MELD-Lactate, CLIF-C ACLF, CLIF-C ACLF-Lactate, and APACHE-II scores for short-term mortality assessment. (ii) to build and validate a novel scoring system and to compare its predictive performance to that of the original five scores. Two hundred sixty-five consecutive cirrhotic patients with ACLF who were admitted to our ICU were enrolled. The prognostic values for mortality were assessed by ROC analysis. A novel model was developed and internally validated using fivefold cross-validation. Alcohol abuse was identified as the primary etiology of cirrhosis. The AUROC of the five prognostic scores were not significantly superior to each other in predicting 1-month and 3-month mortality. The newly developed prognostic model, incorporating age, alveolar–arterial gradient (A-a gradient), BUN, total bilirubin level, INR, and HE grades, exhibited significantly improved performance in predicting 1-month and 3-month mortality with AUROC of 0.863 and 0.829, respectively, as compared to the original five prognostic scores. The novel ACLF model seems to be superior to the original five scores in predicting short-term mortality in ACLF patients admitted to an ICU. Further rigorous validation is required.

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Graphical abstract
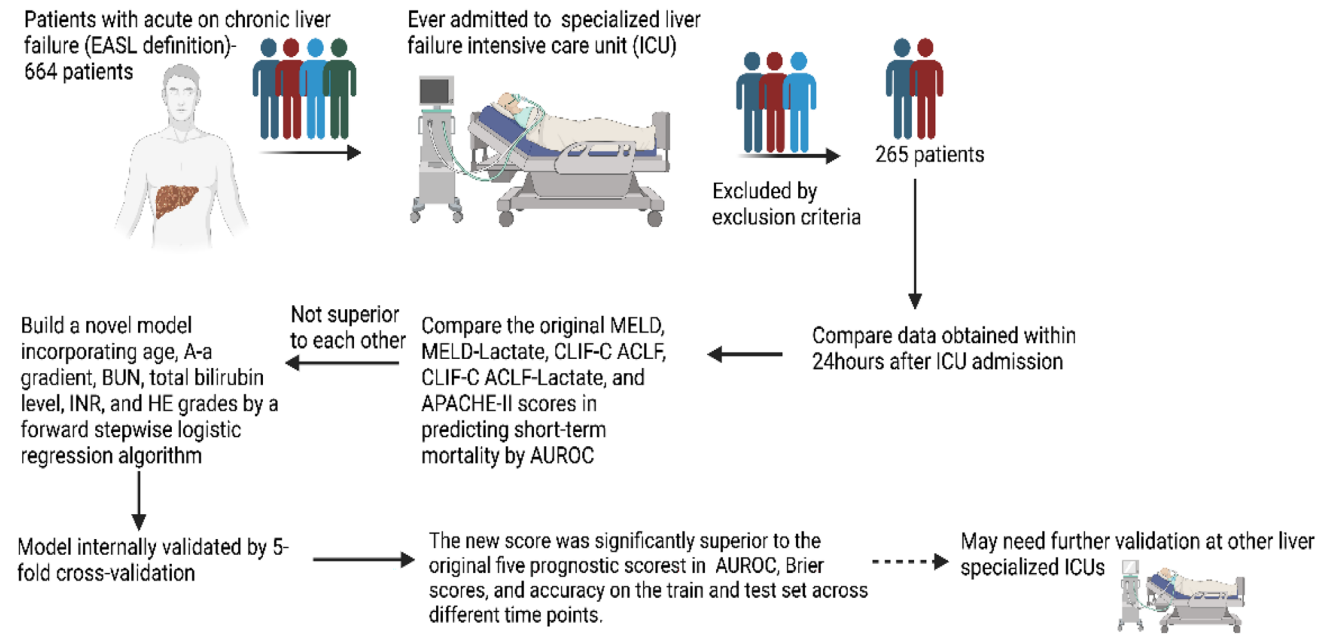
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Background

Patients with liver cirrhosis are at increased risk of acute decompensation, which may lead to organ failure(s) and the development of acute-on-chronic liver failure (ACLF) [1–5]. The high mortality rate associated with the syndrome often necessitates ICU admission [3, 5, 6]. Therefore, expertise in both hepatology and critical care is crucial in the intensive care management of these patients for optimizing recovery outcomes. However, some patients are at a heightened risk of rapid clinical deterioration, necessitating urgent liver transplantation (LT) [6, 7]. Due to the short transplantation window, a rapid decision-making process is necessary [6, 7].

Two important issues for a successful bridging to LT are accurate prognostication and prioritization of ACLF patients awaiting LT [6]. Therefore, it is essential to develop an accurate prognostic score to estimate the outcomes in ACLF patients and help guide clinicians in determining the appropriate treatment options according to the predicted outcomes [8].

Despite the development of several prognostic scoring systems for evaluating outcomes and organ dysfunction in ICU patients [9, 10], accurately predicting short- and long-term mortality remains a significant challenge [11]. The

European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium developed the CLIF Consortium ACLF score (CLIF-C ACLFs) by simplifying the original CLIF-Sequential Organ Failure Assessment (SOFA) score based on CLIF-C organ failure (OF) scores, which demonstrated higher prognostic accuracy than the CLIF-SOFA, the Model for End-Stage Liver Disease (MELD), MELD-Na, and Child–Pugh (CP) scores [12] for ACLF patients. It was also externally validated in ACLF patients hospitalized in a single ICU [12]. The CLIF-C ACLF-D score was derived from the Predicting Acute-on-Chronic Liver Failure (PREDICT) study [13]. The newly devised score predicts the likelihood of ACLF occurrence in individuals with acute decompensation within 3 months of hospitalization. The score demonstrates comparable precision and reduced variance in comparison to alternative scores, as evidenced by the validation set [13].

Several generations of the acute physiology and chronic health evaluation (APACHE) system have been devised, establishing a reliable ICU prognostic tool. The system gauges the severity of illness and general health of adult critically ill patients [14–16]. The APACHE model demonstrated exceptional predictive precision in adjusting for mortality risk in the ICU [17]. The Child–Turcotte–Pugh

(CTP) score and the MELD score are frequently employed prognostic tools in patients with liver cirrhosis. They have been utilized as key determinants in allocating donor livers in the United States since February 2002 [18–20]. Furthermore, several scoring systems have been developed to predict mortality in ACLF, including the MELD-Lactate score [21], and the CLIF ACLF-Lactate score [11].

However, limited research has been conducted to compare ICU prognostic scores with liver failure scores in individuals with ACLF. The optimal prognostic scoring system for predicting overall mortality in ICU-admitted ACLF patients remains uncertain. In addition, it is intriguing whether a new model could be created to outperform the pre-existing prognostic scores. Therefore, our primary objective was to compare the prognostic capabilities of the original MELD, MELD-Lactate, CLIF-C ACLF, CLIF ACLF-Lactate, and APACHE-II scores for predicting short-term mortality, specifically 1-month and 3-month mortality in ACLF patients. Second, a novel predicting scoring system was developed and tested for its superiority over the original five scoring systems in predicting short-term mortality among ACLF patients admitted to the ICU.

Methods

ACLF diagnosis and grading

ACLF diagnosis was established according to the diagnostic criteria specified by the EASL-CLIF Consortium. The EASL-CLIF Consortium criteria were used to assess the severity of ACLF [1, 12]. ACLF grade 1 is defined by either (a) the presence of a single organ failure (e.g., hepatic, coagulation, circulatory, or pulmonary) accompanied by a serum creatinine level of 1.5–1.9 mg/dL and/or West-Haven grade 1 or 2 hepatic encephalopathy; or (b) single renal failure (creatinine level ≥ 2.0 mg/dL) in the absence of other organ failure; or (c) single brain failure with a serum creatinine level of 1.5–1.9 mg/dL. ACLF 2 was characterized by two organ failures, while ACLF 3 was characterized by the presence of three or more organ failures.

Patient selection

This study included cirrhotic patients with acute decompensation (AD) admitted to the hepato-gastroenterology ICU of our hospital between November 2013 and December 2019, meeting the inclusion criteria. Patients who were under age 18 years old, had pre-existing hepatocellular carcinoma or other cancers with/without liver metastasis, were pregnant, had undergone orthotopic liver transplantation before or during ICU admission, or follow-up, had ACLF score of 0, could not be classified into ACLF grades 1/2/3, and did

not have available serum lactate levels within 24 h of ICU admission were excluded from the analysis. The study design and patient selection flow chart are presented in Fig. 1.

Definition of liver cirrhosis and its acute decompensation

Liver cirrhosis was diagnosed through histopathological confirmation or a composite of compatible clinical features, laboratory tests, endoscopic findings, as well as radiological imaging [11, 22–24]. Acute decompensation of cirrhosis is associated with severe and life-threatening complications, such as variceal bleeding, refractory ascites, sepsis, hepatic encephalopathy, or spontaneous bacterial peritonitis [22, 23].

Data source and collection

Data were collected retrospectively from the medical records of patients admitted to the hepato-gastroenterology ICU at Chang-Gung Memorial Hospital, Linkou medical center. This included patient demographics, etiology of cirrhosis, laboratory test results, vital signs, Glasgow coma scale score, urine output, oxygenation support, mechanical ventilator settings, and survival interval. Data were collected within 24 h of ICU admission and scored using appropriate formulas.

Primary, secondary outcomes, and scheduled follow-up periods

The primary outcomes were mortalities at 1 month and 3 months. Secondary outcomes were in-hospital, 6-month, and 12-month mortality. Survival of patients after discharge was confirmed through telephone interviews and/or analysis of medical records. Each patient was followed until the date of death or February 28th, 2022, whichever came first. Because patients who underwent liver transplantation during the study were excluded from the analysis, a completing risk analysis was not performed.

Calculation of prognostic scores

Prognostic scores were calculated using their respective formulas proposed in previous studies. The MELD score was $11.2 \times \ln$ [international normalized ratio (INR)] $+ 9.57 \times \ln$ (creatinine, mg/dL) $+ 3.78 \times \ln$ (bilirubin, mg/dL) $+ 6.43$), with a lower bound of 1 for all three variables and an upper bound of 4 for serum creatinine [25]. MELD-Lactate $= 0.251 + 5.5257 \times$ sqrt(lactate) $+ 0.338 \times$ MELD [21]. The CLIF-C ACLF score $= 10 \times [0.33 \times$ CLIF-OFs $+ 0.04 \times$ Age $+ 0.63 \times \ln$ (WBC count) $- 2]$ [12]. The lactate-adjusted CLIF-C ACLF (CLIF-C ACLF-Lactate

Fig. 1 Flow chart demonstrating the process for patient recruitment, inclusion, and exclusion of ACLF cases in the intensive care unit (ICU). AD: acute decompensation
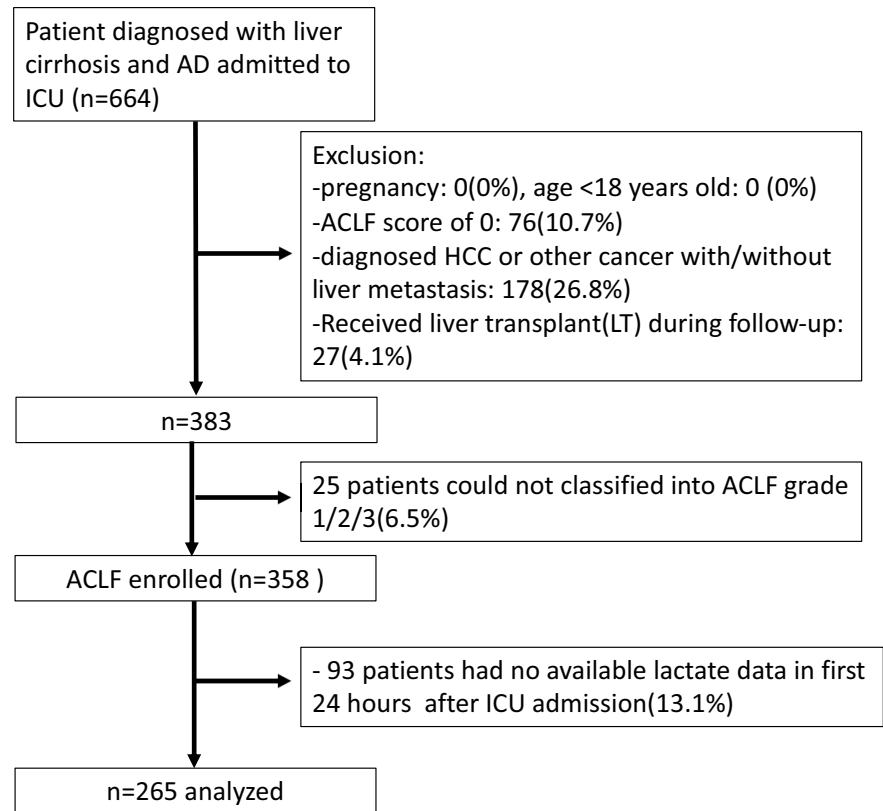
score) = CLIF-C ACLFs + 8 × ln (lactate) − 7 [26]. The APACHE-II score was calculated according to the study by Knaus WA, et al [27].

Statistical analysis

Continuous variables were presented as mean ± SD or median and interquartile range (IQR 25–75 percentile) depending on their distribution, and comparisons were made using the Independent Student *t* test for normal distributions and the Mann–Whitney U test for non-normal distributions. Categorical variables were presented as frequencies and percentages, and their comparison was performed using the Chi-square test. Fisher's exact test was used in cases where more than 20% of the statistic cells had an expected frequency of less than 5. The novel model's predictive ability was assessed by determining the area under the receiver operating characteristic curve (AUROC) and compared with MELD, MELD-Lactate, CLIF-C ACLF, CLIF-C ACLF Lactate, and APACHE-II scores. A competing risk analysis was not performed as the number of patients who received liver transplantation during follow-up was too small and had been excluded from the analysis. The predictive performance of each score to predict mortality was compared using the Delong test. Statistical analyses were performed using IBM SPSS Statistics 26 (SPSS Inc., Chicago, IL, USA) and a *p* value < 0.05 was considered significant.

Novel prognostic model building

Using the current dataset, mortality at different time points (i.e., 1 month, 3 months, etc.) was the dependent variable (Supplementary Table 1). The initial model considered several independent variables, including patients' demographics, etiology of cirrhosis, hemograms, serum biochemistry tests, vital signs (body temperature, blood pressure, respiratory rate, and heart rate), oxygenation support, mechanical ventilator setting, Glasgow coma scale (GCS) score, and urine output. Variables with *p* < 0.20 in the univariate analysis were entered in a multivariate logistic regression analysis [28] to identify independent predictors associated with the primary and secondary outcomes and to select variables that could predict mortality at different time points with an AUROC > 0.8 [21]. As shown in Supplementary Table 1, Model 1, 2, and 3 were, thus, obtained and were further evaluated by their performance [29]. Finally, Model 3 was found to have the highest AUROC across different time points and was, therefore, chosen as our new prediction model (Supplementary Table 1).

Model validation

For model validation, internal validation by fivefold cross-validation was performed. This method divides the dataset into 5 subsets of 80/20 splits (folds) where

each 80%-fold is used as the training set for the remaining 20%. Summary statistics for this procedure include the AUROC, Brier scores, and accuracy at intervals. As revealed in Supplementary Table 2, the new model had a good performance of AUC, Brier scores, and accuracy on the train and test set across different time points.

Results

Patients' baseline characteristics

A total of 265 cirrhotic patients with ACLF were enrolled from November 2013 to December 2019 and followed until February 2022 (Fig. 1). Table 1 displays the baseline characteristics of the 265 patients. The overall mean age was 55.2 ± 13.3 years old. Two hundred five patients (77.4%) were male. The main etiology of cirrhosis in all patients was alcohol abuse (152 patients, 57.4%). The second most common etiology was hepatitis B virus infection (56 patients, 21.1%), followed by hepatitis C virus infection (37 patients, 14.0%) and other etiologies including non-alcoholic steatohepatitis (NASH) and autoimmune hepatitis. In addition, upper gastrointestinal bleeding (131 patients; 49.4%) accounted for the major indication for ICU admission. The mean follow-up period was 1.6 years. The 1-month mortality rate was 35.8% (95/265). The in-hospital mortality rate was 45.7% (121/265). The 3-month mortality rate was 50.2% (133/265). The 6-month mortality rate was 59.2% (157/265). The 1-year mortality rate was 65.3% (173/265). The overall mortality rate was 72.4% (192/265).

For survivor patients, the main indication for ICU admission was upper GI bleeding (53 patients, 72.6%), while the main indication for ICU admission was sepsis (98 patients, 51.0%) in non-survivor patients.

In the non-survivor group, A-a gradient, respiratory rate, white cell count, INR, serum bilirubin, serum blood urea nitrogen, serum creatinine, serum glucose, and serum lactate were significantly higher than in the survivor group. Conversely, arterial pH, body temperature, and serum albumin were significantly higher in the survivor group than in the non-survivor group. The non-survivor group had significantly higher proportions of patients with PaO2/FiO2≦200 and grade III/IV hepatic encephalopathy compared to the survivor group. In contrast, the survivor group had a significantly higher proportion of patients without hepatic encephalopathy compared to the non-survivor group. Non-survivors had a higher frequency of ACLF grade 3 classification for severity assessment.

Comparison of the predictive strength of the original five prognostic scores for the primary outcomes

The AUROCs of the original five prognostic scores (MELD, MELD-Lactate, CLIF-C ACLF, CLIF ACLF-Lactate, APACHE-II) were compared concurrently to predict the primary outcomes. As shown in Table 2 and Fig. 2a, the AUROC (95% confidence intervals) of the five prognostic scores for 1-month mortality prediction was 0.818 (0.763–0.872), 0.783 (0.727–0.839), 0.787 (0.728–0.846), 0.793 (0.736–0.849), and 0.764 (0.705–0.823) respectively. The AUROC analysis did not demonstrate significant superiority of any of the five prognostic scores over the others in predicting 1-month or 3-month mortality (Table 3 and Fig. 2b).

Comparison of the predictive strength of the original five prognostic scores for the secondary outcomes

The AUROCs of the original five prognostic scores were simultaneously compared to predict secondary outcomes. Likewise, these five prognostic scores were still not significantly superior to each other in the in-hospital, 6-month, and 1-year mortality (Supplementary Fig. 1 and Supplementary Table 3).

Novel model building and validation

Since the original five prognostic models were not superior to each other, a novel model was built and validated, which was mentioned in the patient and method section (see Supplementary Table 1 and Supplementary 2).

The formulas of the novel model to predict the primary outcomes are:

(1) One-month mortality $= -6.741 + 0.035$ (age) $+ 0.002$ (A-a gradient) $+ 0.009$ (BUN) $+ 0.07$ (total bilirubin) $+ 1.015$ (INR) $+ \beta n$ (HE GRADE n), $[1 \leqq n \leqq 4, n = 1, \beta n = 0.871; n = 2, \beta n = 0.913; n = 3, \beta n = 0.77; n = 4, \beta n = 1.516]$.

(2) Three-month mortality $= -5.588 + 0.032$ (age) $+ 0.002$ (A-a gradient) $+ 0.012$ (BUN) $+ 0.038$ (total bilirubin) $+ 1.069$ (INR) $+ \beta n$ (HE GRADE n), $[1 \leqq n \leqq 4, n = 1, \beta n = 0.638; n = 2, \beta n = 0.631; n = 3, \beta n = 0.764; n = 4, \beta n = 0.681]$

The formulas for predicting in-hospital, 6-month, and 1-year mortality as the secondary outcomes are presented in Supplementary Table 4.

Table 1 Demographics of 265 patients with ACLF admitted to ICU

Patients' characteristics	All patients (265 patients)	Survivors[a] (73 patients)	Non-survivors[a] (192 patients)	p value
Age (mean ± SD years)	55.21 ± 13.35	51.25 ± 11.55	56.71 ± 13.71	0.003
Gender = male	205 (77.4%)	57 (78.1%)	148 (77.1%)	0.862
Etiology				
HBV	56 (21.1%)	11 (15.1%)	45 (23.4%)	0.136
HCV	37 (14.0%)	6 (8.2%)	31 (16.1%)	0.096
ALC	152 (57.4%)	51 (69.9%)	101 (52.6%)	0.011
Other[b]	20 (7.5%)	5 (6.8%)	15 (7.8%)	0.791
Clinical parameters				
Arterial pH	7.4 ± 0.13	7.44 ± 0.09	7.38 ± 0.14	< 0.001
PaO2/FiO2 > 300	128 (48.3%)	42 (57.5%)	86 (44.8%)	0.012
PaO2/FiO2 = 200–300	78 (29.4%)	22 (30.1%)	56 (29.2%)	0.877
PaO2/FiO2 ≤ 200	59 (22.3%)	9 (12.3%)	50 (26.0%)	0.017
A-a gradient (mmHg)	183.77 ± 149.78	126.96 ± 109.99	205.37 ± 157.31	< 0.001
MAP (mmHg)	87.18 ± 19.91	56.43 ± 16.97	86.32 ± 20.89	0.256
Temperature (℃)	36.55 ± 1.25	36.9 ± 1.14	36.42 ± 1.27	0.005
Respiratory rate (/min)	19.95 ± 5.2	18.74 ± 4.13	20.42 ± 5.49	0.008
Use of vasopressors	203 (76.6%)	58 (79.4%)	145 (75.5%)	0.499
No HE	96 (36.2)	43 (58.9%)	53 (27.6%)	0.003
HE I-II	101 (38.1%)	25 (34.2%)	76 (39.6%)	0.424
HE III-IV	68 (25.7%)	5 (6.8%)	63 (32.8%)	< 0.001
White cell count (× 1000/μL)	11.54 ± 9.23	9.04 ± 4.71	12.50 ± 10.31	< 0.001
Hematocrit (mg/dL)	26.96 ± 6.74	26.91 ± 6.71	26.99 ± 6.76	0.931
INR	2.14 ± 1.18	1.68 ± 0.59	2.31 ± 4.3	< 0.001
Serum bilirubin (mg/dL)	8.85 ± 10.42	5.57 ± 7.66	10.09 ± 11.05	< 0.001
Serum BUN (mg/dL)	40.07 ± 29.84	25.45 ± 20.45	45.63 ± 30.99	< 0.001
Serum creatinine (mg/dL)	1.91 ± 1.56	1.41 ± 1.21	2.10 ± 1.64	0.001
Serum sodium (mEq/L)	138.28 ± 7.94	137.62 ± 4.81	138.53 ± 8.84	0.286
Serum glucose (mg/dL)	183.57 ± 86.86	165.14 ± 75.27	190.57 ± 90.07	0.021
Albumin (g/dL)	2.6 ± 0.56	2.84 ± 0.52	2.51 ± 0.54	< 0.001
Lactate (mmol/L)	4.77 ± 4.46	3.88 ± 3.56	5.11 ± 4.72	0.044
Mechanical Ventilation use	162 (61.1%)	32 (43.8%)	130 (67.7%)	< 0.001
ACLF grades of EASL-CLIF Consortium				
ACLF 1	60 (22.6%)	32 (43.8%)	28 (14.6%)	< 0.001
ACLF 2	87 (32.8%)	25 (34.2%)	62 (32.3%)	0.762
ACLF 3	118 (44.5)	16 (21.9%)	102 (53.1%)	< 0.001
Indications for ICU admission				
Gastrointestinal bleeding	131 (49.4%)	53 (72.6%)	78 (40.6%)	< 0.001
HBV or HCV acute exacerbation	16 (6%)	3 (4.1%)	13 (6.8%)	0.416
Sepsis	114 (43%)	15 (20.5%)	98 (51.0%)	< 0.001
Other	5 (1.8%)	2 (2.7%)	3 (1.6%)	0.748
Score on admission to ICU mean (range)				
CTP	9.77 ± 2.09	8.64 ± 1.83	10.2 ± 2.02	< 0.001
MELD	24.45 ± 11.24	18.86 ± 9.64	26.57 ± 11.09	< 0.001
MELD-Lactate	19.77 ± 6.6	16.84 ± 5.74	20.89 ± 6.58	< 0.001
CLIF-C OFs	11.72 ± 2.39	10.45 ± 2.11	12.2 ± 2.32	< 0.001
CLIF-C ACLF	54.84 ± 10.61	48.13 ± 9.28	57.39 ± 9.97	< 0.001
CLIF-C ACLF-lactate	58.23 ± 13.1	50.03 ± 11.91	61.34 ± 12.18	< 0.001
APACHE-II	22.11 ± 7.95	16.9 ± 5.6	24.09 ± 7.83	< 0.001

HE hepatic encephalopathy classified by the West-Heaven criteria, *HBV* chronic hepatitis B virus-related cirrhosis, *HCV* chronic hepatitis C virus-related cirrhosis, *ALC* alcohol-related cirrhosis, *INR* international normalized ratio, *CTP* Child–Turcotte–Pugh (CTP) score

[a]Overall survivors vs. non-survivors

[b]Other etiologies of cirrhosis includes NASH (non-alcoholic steatohepatitis) and autoimmune hepatitis, etc.

Table 2 Comparison of the six prognostic scores to predict 1-month mortality by AUROC with pairwise comparison

		AUROC (95%CI)		Pairwise Sig. Mark					
				A	B	C	D	E	F
MELD	A	0.818	(0.763–0.872)	■					▨
MELD_lactate	B	0.783	(0.727–0.839)		■				▨
CLIF_ACLF	C	0.787	(0.728–0.846)			■			▨
CLIF_ACLF_Lactate	D	0.793	(0.736–0.849)				■		▨
APACHE_II	E	0.764	(0.705–0.823)					■	▨
New Model	F	0.863	(0.818–0.907)	▨	▨	▨	▨	▨	■

AUROC area under receiver operating characteristic curve; the yellow-color marks reflect significant difference in pairwise comparison at significance level ($\alpha = 0.05$) and is more important than the black one

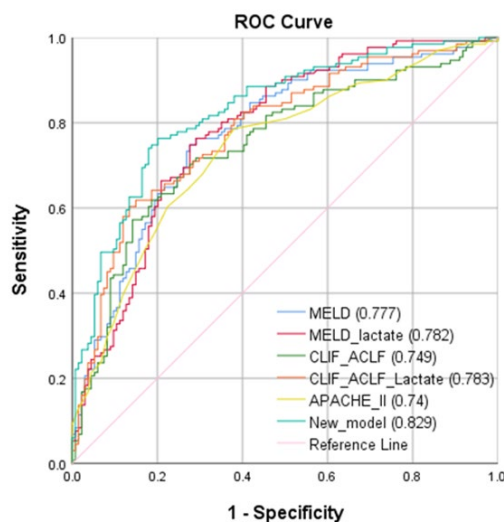2a. one-month mortality
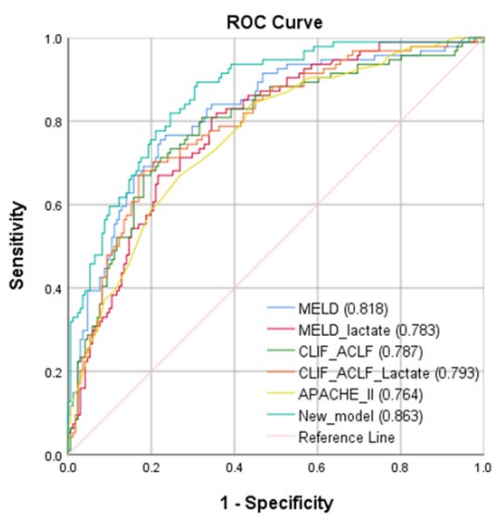
2b. three-month mortality

Fig. 2 Comparison of the new model and the five prognostic scores predicting short-term mortality by AUROC analysis, (a) 1-month mortality (b) 3-month mortality

Comparison of the predictive strength of the original five prognostic scores with the novel model for the primary and secondary outcomes

First, the AUROCs of the original five prognostic scores were compared with the new model concurrently to predict the primary outcomes. Table 2 and Fig. 2a demonstrate that the new model had a higher AUROC (95% confidence intervals) of 0.863 (0.818–0.907) for predicting 1-month mortality, as compared to the original five prognostic scores. The yellow-colored marks in Table 2 indicate significant difference in comparison between the models. Furthermore, the AUROC (95% confidence intervals) of the new model in predicting 3-month mortality was 0.829 (0.780–0.879), which was also superior to all the original five prognostic scores (Table 3 yellow-color marks and Fig. 2b).

The new model's cut-off value for predicting 1-month mortality was – 1.0398, with mortality rates of 7.8% and 62.5% below and above this value, respectively. Similarly, the cut-off value for predicting 3-month mortality was 0.02, with corresponding mortality rates of 25.2% and 81.4% below and above this threshold, respectively.

Second, the predicting strength of the new model was also significantly superior to the original five prognostic scores in predicting in-hospital, 6-month, and 1-year mortalities (Supplementary Table 3 and Supplementary Fig. 2).

Subgroup sensitivity analysis was also conducted. The analysis included 131 patients who were admitted to ICU due to UGI bleeding and 114 patients who were admitted to ICU due to sepsis. The AUROC of the 1-month mortality prediction was 0.866 in the UGI bleeding subgroup and 0.800 in the sepsis subgroup.

Discussion

Prior research has shown the reliability and superiority of the CLIF-C ACLF score as an alternative prognostic scoring system for ACLF patients [30–33]. However, the superiority

Table 3 Comparison of the six prognostic scores to predict 3-month mortality by AUROC with pairwise comparison

		AUROC	(95%CI)	A	B	C	D	E	F
					Pairwise Sig. Mark				
MELD	A	0.777	(0.720–0.833)	■					▨
MELD_lactate	B	0.782	(0.727–0.837)		■				
CLIF_ACLF	C	0.749	(0.659–0.809)			■	▨		
CLIF_ACLF_Lactate	D	0.783	(0.728–0.839)			▨	■		▨
APACHE_II	E	0.740	(0.680–0.800)					■	▨
New Model	F	0.829	(0.780–0.879)	▨	▨	▨	▨	▨	■

AUROC area under receiver operating characteristic curve; the yellow-color marks reflect significant difference in pairwise comparison at significance level ($\alpha = 0.05$) and is more important than the black ones

of the CLIF-C ACLF score compared to other prognostic scores in ICU-admitted ACLF patients remains uncertain. In our dataset, the AUROCs of the original five prognostic scores (MELD, MELD-Lactate, CLIF-C ACLF, CLIF ACLF-Lactate, APACHE-II) were compared concurrently to predict the primary and secondary outcomes. The results demonstrated that the five prognostic scores were not significantly superior to each other. Therefore, a novel predicting scoring model was built, internally validated, and tested whether it was superior to the original five prognostic scores in predicting the short-term mortality of ACLF patients who were admitted to the ICU. In summary, the new model outperformed the five prognostic scores in predicting mortality at various time points. Although this novel model may require further external validation, it remains a potentially excellent tool for assessing the short-term outcomes in ICU-admitted ACLF patients.

In this novel model, independent variables consist of age, A-a gradient, BUN, total bilirubin level, INR, and HE grades. These variables have been shown to be associated with the mortality of ACLF patients in several studies. First, age, serum total bilirubin level, INR, and HE grades are also included in the CLIF-C ACLF score [12]. Clinicians should be especially alert to the rapid progression and higher mortality rate of HE in ACLF patients [34, 35]. In addition, an elevated alveolar–arterial gradient (A-a) gradient can also be observed in patients with cirrhosis and/or portal hypertension who have developed hepatopulmonary syndrome. [36, 37]. Furthermore, acute kidney injury is an important predictor of early mortality in patients ACLF [38]. A study has indicated that serum urea is a more accurate predictor of mortality than serum creatinine in ACLF patients with acute kidney injury [39]. In critically ill patients, an elevated BUN was associated with increased mortality independent of serum creatinine [40]. Further studies on the relationship between the variables and acute-on-chronic liver failure (ACLF) are necessary to enhance understanding and improve patient outcomes.

Accurately identifying the most effective prognostic tool for ICU-admitted ACLF patients is crucial for reducing the higher short- and long-term mortality rates associated with this patient population. Consequently, more aggressive treatment modalities, such as liver transplantation, are often considered [6, 7]. This is particularly relevant in East Asia, where HBV-related ACLF is prevalent [41, 42]. However, due to the implementation of effective anti-viral agents against HBV and HCV in recent years [41], alcohol-associated cirrhosis has contributed up to 50% of the overall cirrhosis burden in the United States and worldwide nowadays [43, 44]. It was comparable to our study population (alcoholic-related cirrhosis accounted for 57.4%). Treatment of alcoholic cirrhosis and ACLF may be an important issue in Asia and the world in the future [45–47]. The novel model can aid hepatologists and intensivists in predicting prognosis more accurately, enabling early identification of high-risk patients who may benefit from liver transplantation [48, 49].

However, our study has some limitations. First, the novel model has not been extensively validated. Further collaboration with other ICUs is urgently needed. Second, APACHE III and IV were not adopted for comparison due to their complexity. Third, data in this study were collected within 24 h of ICU admission, while the CANONIC study collected data between days 3 and 7 to calculate the CLIF-C ACLF score. However, collecting data on the first day of ICU admission was done to ensure consistency. Data obtained at different time points for calculating these prognostic scores may lead to different results. Fourth, MELD and MELD-Lactate, although not originally developed for ACLF patients, were included in this study due to their clinical utility in assessing the prognosis of patients with end-stage liver disease. Fifth, variables remained consistent in our novel model, whereas constants exhibited variation in predicting mortality at 1-month, in-hospital, 3-month, 6-month, and 1-year intervals. Conversely, five other prognostic scores maintained uniform variables and constants across distinct periods of mortality prediction.

Conclusion

The original five prognostic scores (MELD, MELD-Lactate, CLIF-C ACLF, CLIF ACLF-Lactate, APACHE-II) were not significantly superior to each other in predicting short-term mortality among these critically ill cirrhotic patients complicated with ACLF who were admitted to a hepatology ICU. The novel model incorporating age, A-a gradient, BUN, total bilirubin level, INR, and HE grades was significantly superior to the original five prognostic scores in predicting mortalities at different time points. This novel model may require further external validation, but remains a potentially excellent tool for assessing the short-term outcomes in ACLF patients who were admitted to the ICU.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval and consent to participate The Institutional Review Board of Linkou Chang Gung Memorial Hospital approved the study (202000112B0).

Consent for publication This manuscript contains no individual persons' data, so the Institutional Review Board has waived the need for informed consent.

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