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Utility of prognostic scores in predicting short-term mortality in patients with acute-on-chronic liver failure

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Abstract

Background: Acute-on-chronic liver failure (ACLF) is a distinct syndrome associated with high short-term mortality. Early identification of patients at high risk is essential to determine emergency for transplantation and decide and prioritize the need for intensive care unit (ICU). We aimed to evaluate the performance of the different prognostic scores in the prediction of in-hospital mortality in patients with ACLF. A total of 249 patients with ACLF were included and followed till discharge from the hospital. Univariate and Cox regression analyses were used to assess the performance of liver-specific (Child-Pugh and MELD) and ACLF prognostic scores (CLIF-C OF, CLIF-SOFA, CLIF-C AD, CLIF-C ACLF) in the prediction of in-hospital mortality.

Results: Patients were mostly males (71.1%) with a mean age of 53.9 ± 12.8 years. The etiology of pre-existing liver disease was HCV in 57.8%. Sepsis was the most common precipitating factor (49.8%) and the mortality rate was 74.3%. In univariate analysis, all scores were significantly higher in the deceased group ($P<0.0001$). AUROC were 0.897, 0.884, 0.870, 0.861, 0.861, and 0.850 for CLIF-C OF, CLIF-C AD, CLIF-C ACLF, Child-Pugh, CLIF-SOFA, and MELD scores, respectively. In multivariate analysis, 2 independent predictors of mortality were identified: CLIF-C ACLF score (*OR* 3.25, 95% *CI* 1.03–10.25, $P<0.0001$) and Child-Pugh class C (*OR* 1.04, 95% *CI* 1.02–1.06, $P=0.044$).

Conclusions: All the studied scores could predict in-hospital mortality of patients with ACLF. However, CLIF-C ACLF and Child-Pugh class performed better as they could significantly and independently predict mortality.

Keywords: ACLF, CLIF-C OF, CLIF-C AD, CLIF-C ACLF, CLIF-SOFA, Child-Pugh, MELD

Background

Acute-on-chronic liver failure (ACLF) is a distinct syndrome that occurs in patients with chronic liver disease, with or without cirrhosis, characterized by acute decompensation of the liver (ascites, encephalopathy, gastrointestinal bleeding, and/or bacterial infection) and one or more extrahepatic organ dysfunction (kidney, brain, coagulation, circulation, and/or lung), with a high short-term mortality of 33% at 28 days and 51% at 90 days [1].

Even though many definitions for ACLF have been evolved, the most important definitions in clinical practice are from the Asian Pacific Association for the Study of Liver (APASL), American Association for the Study of Liver (AASLD), European Association for the Study of Liver (EASL), and World Gastroenterology Organization (WGO) [2].

In the majority of patients, ACLF is precipitated by an acute event, which provides an inflammatory burst to the background chronic inflammation that is present in patients with cirrhosis and decompensation. The resulting surge in inflammatory mediators leads to organ failure through many mechanisms including organ hypoperfusion [3]. However, in up 40% of patients with ACLF, no acute event can be identified prior to the development of ACLF [1]. ACLF is associated with features of systemic inflammation. Excessive

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release of pro-inflammatory cytokines and chemokines "cytokine storm" by the patient's immune system seems to be the key operating mechanism responsible for tissue damage and organ failure [4, 5].

Compared to ACLF, decompensated cirrhosis without ACLF lacks organ failure. Organ failure could be defined by the significantly impaired function of the liver, kidneys, brain, coagulation, and circulatory and respiratory systems which could predict mortality [6].

In spite of this catastrophic presentation and outcome, there is a component of potential reversibility with adequate support and management of the precipitating factor [7].

A universally accepted prognostic model for ACLF is lacking due to discrepancies and unevenness in the definition of ACLF. Many already widely used prognostic models for cirrhosis have been applied for the evaluation of this syndrome [8–10]. In this regard, prognosis scores can be categorized in two: first that evaluates the severity of liver dysfunction (Child-Pugh, Model of end-stage liver disease "MELD") [11] and second, global prognostic scores (Acute Physiology and Chronic Health Evaluation "APACHE II" [12, 13] and sequential organ failure assessment "SOFA") [14, 15]. Although several lines of evidence demonstrate that global prognostic scores are superior to liver-specific scores for estimation of prognosis in these patients, the optimum scores with the highest performance have not been enough explored yet.

In the current study, we aimed to compare the currently available prognostic scores to predict short-term mortality to early identify patients at high risk who will require specific treatments, intensive management, or emergency liver transplantation.

Methods

Study setting and inclusion

The current study was carried out on all patients who met the definition of ACLF according to the EASL-Chronic Liver Failure consortium (EASL-CLIF) and who were admitted to the National Liver Institute hospital in the period between April 1, 2018, and March 31, 2019. Inclusion criteria were patients with stable pre-existing liver disease who developed acute hepatic decompensation (hepatic encephalopathy, variceal hemorrhage, large ascites, bacterial infections, or any combination of these) after exposure to an identifiable or non-identifiable acute insult and associated with organ(s) failure (liver, kidney, brain, circulatory, coagulation, or respiratory failure).

Definitions

Like CANONIC study, organ failure was defined as the following: liver failure: hyperbilirubinemia of $\geq$ 12.0 mg/dl; renal failure: serum creatinine level of $\geq$ 2 mg/dl; brain failure: hepatic encephalopathy grade III/IV as per West Haven criteria; coagulation failure: international normalized ratio (INR) > 2.5 and/or a platelet count $\leq 20 \times 10^9$ /L; circulatory failure: the use of dopamine, dobutamine, or terlipressin; and respiratory failure: partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) ratio $\leq$ 200 or pulse oximetric saturation (SpO2) to FiO2 ratio $\leq$ 200 [1].

According to the CLIF-OF score, ACLF was graded into 3 grades: ACLF grade 1: patients with single kidney failure or non-renal single organ failure (liver, lung, coagulation, or circulatory) associated with renal dysfunction (creatinine 1.5–1.9 mg/dl) and/or brain dysfunction (grade 1 or 2 hepatic encephalopathy), ACLF grade 2: patients with two organ failures, and ACLF grade 3: patients with three or more organ failures.

Exclusion criteria

Patients with one or more of the following were excluded: prior organ transplantation, hepatocellular carcinoma (HCC), extrahepatic malignancies, and severe chronic extrahepatic diseases.

Workup

Included patients were subjected to thorough history taking and clinical examination, abdominal ultrasonography, routine laboratory investigations (CBC, liver and renal biochemical tests). Workup to identify the etiology of the acute liver insult causing ACLF was done. This panel included the routine markers for viral hepatitis and polymerase chain reactions (PCRs) for hepatitis viruses (HCV RNA, HEV RNA, HDV RNA, and HBV DNA) when the routine markers were negative. Patients who were negative for viral hepatitis were next tested for hepatitis auto-antibodies, including antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver kidney microsomal antibody (LKM), and total IgG. Wilson's disease workup was done if both virology and autoimmune profiles were negative, including ceruloplasmin and slit-lamp examination for Kayser-Fleisher ring. Rousel Uclaf Causality Assessment Method "RUCAM" scale was used when drug-induced liver injury "DILI" was suspected as a precipitating insult [16]. On admission, hepatic encephalopathy was diagnosed and graded using the West Haven criteria [17]. Data were collected and the following scores were calculated: Child-Pugh [18], MELD [19], CLIF-consortium organ failure (CLIF-C OF) [1], CLIF-C ACLF [20], CLIF-SOFA [15], and CLIF-C

acute decompensation (CLIF-C AD) [21]. Patients were prospectively followed up for in-hospital survival outcome and were categorized into two groups: deceased and improved. Predictors of mortality were statistically analyzed.

A written informed consent was obtained from each eligible patient or his relatives before inclusion. The study protocol was consistent with the ethical principles of the Declaration of Helsinki (1975) and has been approved by the local Institutional Review Board of the National Liver Institute, Menoufia University.

Statistical methods

A univariate analysis of mortality was performed for baseline variables and scores using the chi-square (or if appropriate, Fisher's exact) test and independent samples *t*-test for categorical and quantitative variables, respectively. A multivariate analysis of the significant factors related to mortality, from the univariate analysis, was carried out with a backward stepwise Cox regression approach to identify those variables that independently predicted mortality. The discriminative ability of the liver-specific (Child-Pugh and MELD) and ACLF prognostic scores (CLIF-C OF, CLIF-SOFA and CLIF-C AD, ACLF-C ACLF) and ACLD grades at baseline was evaluated using the area under a receiver operating characteristic (ROC) curve (AUROC). Significance was tested two-sided and set to a *P*-value of less than 0.05. Statistical analyses were performed using IBM SPSS Statistics for Macintosh, version 22.0 (IBM Corp, Armonk, NY, USA).

Results

Baseline characteristics of the studied patients

Two hundred eighty-three patients were hospitalized with ACLF in the period between 1 April 2018 and 31 March 2019. Among them, only 249 patients fulfilled the inclusion and exclusion criteria and were included in the present study. Figure 1 represents the flowchart of the study.

The baseline characteristics are presented in Tables 1 and 2. Most of the patients were males ($n = 177$, 71%) with a mean age of 53.9 ± 12.8 years. The main underlying etiology of chronic liver disease was HCV ($n = 144$, 57.8%). Sepsis was the main precipitating factor of ACLF (n=124, 49.8%), whereas the precipitating factor could not be identified in 30.9% of patients (n=77). Spontaneous bacterial peritonitis (SBP) was the most common type of infection (n=43, 34.7%). Chest infection came as the second most common infection (n=38, 30.6%) followed by urinary tract infection (n=14, 11.3%). Cellulitis was reported in 3 patients (2.4%) while the site of infection could not be determined in 26 patients (21%). On admission, the mean Child-Pugh, MELD, CLIF-C AD, CLIF-C ACLF and CLIF-C OF scores were 11.8 ± 1.5 (mostly class C, 92.8%), 17.3 ± 4.3, 70.9 ± 14.2, 52.4 ± 9.8 and 10.6 ± 2.0 respectively. ACLF grades of the studied patients were as follows: grade 1: n=89, 35.7%; grade 2: 109, 43.8%; and grade 3: 51, 20.2%. As regards ACLF grade, 89 patients (35.7%) were ACLF grade 1, 109 (43.8%) were ACLF grade 2 whereas 51 (20.2%) were ACLF grade 3. Most of the patients needed an initial admission to the ICU (n=191, 76.7%). The mean total stay in the ICU was 7.8 ± 5.6 days and in the hospital was 11.9 ± 7.7 days. At discharge, 185 (74.3%) patients were deceased.

Univariate analysis of in-hospital mortality

The results of the univariate analysis of variables associated with in-hospital mortality are presented in Tables 3 and 4. Deceased patients were significantly older (55.0 vs. 50.7 years, P=0.022) and had significantly lower baseline albumin (2.3 vs. 2.7 g/dl, P<0.0001), platelets (134.5 vs. 163.9 × 10^3/mm^3, P=0.034), Na (123.7 vs. 132.4 mEq/l, P<0.0001), and mean arterial pressure (MAP, 70.4 vs. 79.7 mmHg, P<0.0001). They also had significantly higher baseline INR (2.2 vs. 1.7, P<0.0001), creatinine (3.2 vs. 1.4 mg/dl, P<0.0001), and peripheral leucocytes (15.2 vs. 11.3 × 10^3/mm^3, P<0.0001). The total ICU stay was significantly shorter in patients who died at discharge (6.8 vs. 10.8 days, P<0.0001). However, the total hospital stay did not differ between both groups (P=0.937).

All the studied scores were significantly (P<0.0001) higher in the deceased group, including the Child-Pugh score and class, ACLF grade, and the MELD, CLIF-C AD, CLIF-C OF, CLIF-SOFA, and CLIF-C ACLF scores.

While most of the patients who improved had no ascites (58.7%) or hepatic encephalopathy (88.9%), most of the deceased patients had mild to moderate ascites (70.8%) and grade I–II hepatic encephalopathy (62.7%) (P<0.0001).

It is to be noted that the gender and etiology of chronic liver disease, total bilirubin, ALT, AST, ALP, GGT, and hemoglobin did not show a statistically significant difference between both groups.

Ability of the studied scores to predict in-hospital mortality

After plotting the ROC curves (Fig. 2), all the studied scores were found to significantly predict in-hospital mortality (P<0.0001). AUROC were 0.897, 0.884, 0.870, 0.861, 0.861, and 0.850 for CLIF-C OF, CLIF-C AD, CLIF-C ACLF, Child-Pugh, CLIF-SOFA, and MELD scores, respectively. In addition, ACLF grade as well as Child-Pugh class (C vs. B) was found to significantly predict mortality (AUROC =0.820, 0.611 and $P < 0.0001$, 0.009, respectively).

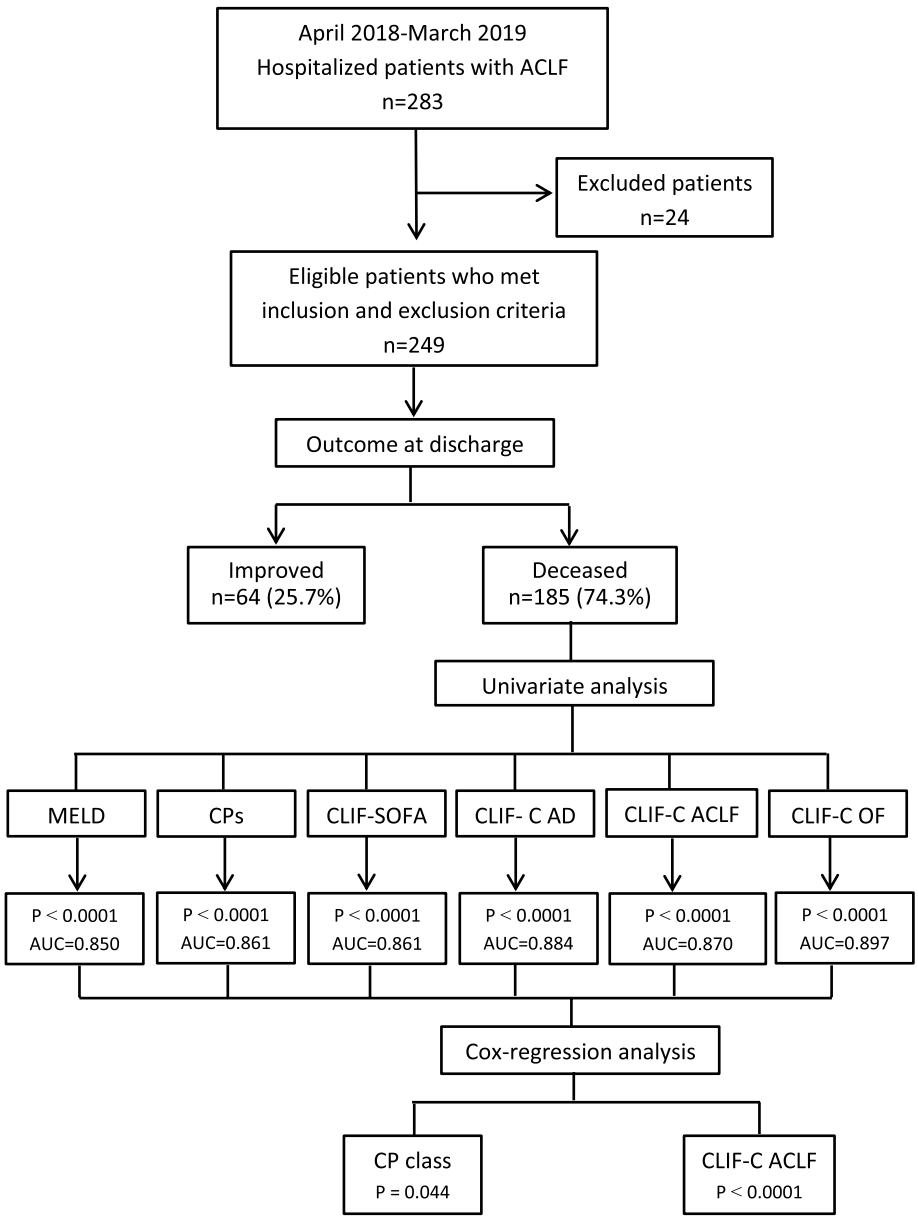

Fig. 1 Flow diagram of the study. Legend: ACLF, acute-on-chronic liver failure; AD, acute decompensation; AUC, area under the ROC curve; CLIF-C, chronic liver failure consortium; CP, Child-Pugh; MELD, model for end-stage liver disease; OF, organ failure; SOFA, Sequential Organ Failure Assessment

Regression analysis for prediction of in-hospital mortality

Using the backward Cox regression, two independent variables were deduced to significantly predict in-hospital mortality (Table 5). Those significant predictors were the CLIF-C ACLF score (*OR* 3.25, 95% *CI* 1.03–10.25, *P*<0.0001) and the Child-Pugh class C vs. B (*OR* 1.04, 95% *CI* 1.02–1.06, *P*=0.044).

Discussion

ACLF is a serious condition associated with a high mortality rate which is 15 times higher as compared to patients with acute decompensation without ACLF [1].

Therefore, it is critical to stratify patients according to prognosis in order to monitor treatment responsiveness, determine emergency for transplantation, and decide allocation in the ICU.

Table 1 Baseline characteristics of the studied patients (quantitative variables)

Variables	Descriptive statistics
Age (years)	53.9 ± 12.8
Bilirubin (mg/dl)	21.3 ± 6.9
Albumin (g/dl)	2.4 ± 0.6
ALT (IU/l)	142 (15–3850)
AST (IU/l)	79 (6–3000)
ALP (IU/l)	151 (41–2080)
GGT (IU/l)	58 (6–1549)
Hemoglobin (g/dl)	10.8 ± 2
WBCs ($\times 10^3/mm^3$)	14.2 ± 7.7
Neutrophils ($\times 10^3/mm^3$)	10.7 ± 2.1
Platelets ($\times 10^3/mm^3$)	141.6 ± 95.3
INR	2.1 ± 0.8
ESR (mm/h)	16.0 ± 7.0
CRP (mg/l)	28.2 ± 5.4
NLR	3.7 ± 1.5
Creatinine (mg/dl)	2.7 ± 2.2
Na (mEq/l)	126 ± 8.9
Systolic BP (mmHg)	98.5 ± 18.9
Diastolic BP (mmHg)	60 ± 13.5
MAP (mmHg)	72.8 ± 14.9
PaO_2(mmHg)	93.3 ± 6.8
Total ICU stay (days)	7.8 ± 5.6
Total hospital stay (days)	11.9 ± 7.7
MELD	17.3 ± 4.3
CLIF-C ACLF score	52.4 ± 9.8
CLIF-C OF score	10.6 ± 2
Child-Pugh score	11.8 ± 1.5
CLIF-C AD score	70.9 ± 14.2
CLIF-SOFA	8.8 ± 1.9

ACLF Acute-on-chronic liver failure, *AD* Acute decompensation, *ALP* Alkaline phosphatase, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *BP* Blood pressure, *CLIF-C* Chronic liver failure consortium, *GGT* Gamma-glutamyl transferase, *ICU* Intensive care unit, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein, *NLR* Neutrophil-lymphocyte ratio, *MAP* Mean arterial pressure, *MELD* Model for end-stage liver disease, *Na* Sodium, *OF* Organ failure, PaO_2 Partial pressure of arterial oxygen, *SD* Standard deviation, *WBCs* White blood cells

In the present study, we have compared the performance of the conventional liver-specific scores (Child-Pugh and MELD) to the widely used international prognostic scores (CLIF-C OF, CLIF-C ACLF, CLIF-SOFA, and CLIF-C AD) in the prediction of in-hospital mortality of patients with ACLF.

Baseline characteristics of the studied patients

The age and gender of the studied patients were comparable to that of the CANONIC study, mean age of 53.9 ± 12.8 vs. 56.0 ± 11.0 years, and 71.1% males vs. 64.4%, respectively [1]. Meanwhile, our studied patients were

Table 2 Baseline characteristics of the studied patients (categorical variables)

Variable	*n* (%)
Sex	
Males	177 (71.1)
Females	72 (28.9)
Precipitating factor of ACLF	
Sepsis	124 (49.8)
Upper GI bleeding	23 (9.2)
De novo AIH	1 (0.4)
AIH flare	8 (3.2)
DILI	9 (3.6)
HBV	2 (0.8)
HCV	1 (0.4)
HDV	2 (0.8)
HEV	1 (0.4)
Wilson's disease	1 (0.4)
Unknown	77 (30.9)
Etiology of pre-existing CLD	
HCV	144 (57.8)
Autoimmune hepatitis	8 (3.2)
Budd-Chiari syndrome	2 (0.8)
HBV	13 (5.2)
HBV-HCV co-infection	1 (0.4)
Unknown	81 (32.5)
Ascites	
No	76 (30.5)
Mild to moderate	154 (61.8)
Marked	19 (7.6)
Hepatic encephalopathy	
No	82 (32.9)
Grades I–II	123 (49.4)
Grades III–IV	44 (17.7)
Initial admission	
Ward	58 (23.3)
ICU	191 (76.7)
Child-Pugh class	
B	18 (7.2)
C	231 (92.8)
ACLF grade	
1	89 (35.7)
2	109 (43.8)
3	51 (20.5)
Outcome	
Improved	64 (25.7)
Deceased	185 (74.3)

ACLF Acute-on-chronic liver failure, *AIH* Autoimmune hepatitis, *CLD* Chronic liver disease, *DILI* Drug-induced liver injury, *ICU* Intensive care unit, *GI* Gastrointestinal, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *HDV* Hepatitis D virus, *HEV* Hepatitis E virus

Table 3 Comparison between improved and deceased groups regarding quantitative variables

	Improved (*n*=64)	Deceased (*n*=185)	*P*
Age (years)	50.7 ± 12.1	55.0 ± 12.9	0.022
Total bilirubin (mg/dl)	20.8 ± 6.7	21.5 ± 7.0	0.482
Albumin (g/dl)	2.7 ± 0.6	2.3 ± 0.5	<0.0001
ALT (IU/l)	113.5 (19–1521)	148 (15–3850)	0.040
AST (IU/l)	83.5 (12–1937)	78 (6–3000)	0.877
ALP (IU/l)	164 (55–663)	149 (6–2080)	0.379
GGT (IU/l)	61 (15–1315)	57 (6-1549)	0.157
Hemoglobin (g/dl)	11.1 ± 1.8	10.7 ± 2.0	0.195
WBCs (×10^3/mm^3)	11.3 ± 6.8	15.2 ± 7.7	<0.0001
Neutrophils (×10^3/mm^3)	7.3 ± 4.1	12.5 ± 4.4	< 0.001
Platelets (×10^3/mm^3)	163.9 ± 108.8	134.5 ± 89.3	0.034
INR	1.7 ± 0.6	2.2 ± 0.9	<0.0001
Creatinine (mg/dl)	1.4 ± 1.9	3.2 ± 2.0	<0.0001
ESR (mm/h)	14.3 ± 5.7	20.2± 5.7	< 0.001
CRP (mg/l)	15.2 ± 6.81	46.6 ± 5.4	< 0.001
NLR	2.2 ± 0.7	5.5 ± 1.6	< 0.001
Na (mEq/l)	132.4 ± 6.1	123.7 ± 8.6	<0.0001
MAP (mmHg)	79.7 ± 9.8	70.4 ± 15.7	<0.0001
Total ICU stay (days)	10.8 ± 6.4	6.8 ± 4.8	<0.0001
Total hospital stay (days)	11.9 ± 7.5	12 ± 7.8	0.937
Child-Pugh score	10.4 ± 1.2	12.3 ± 1.2	<0.0001
MELD	13.3 ± 2.6	18.7 ± 3.6	<0.0001
CLIF-C OF score	8.6 ± 1.2	11.3 ± 1.7	<0.0001
CLIF-C ACLF score	42.8 ± 8.2	55.6 ± 8.0	<0.0001
CLIF-C AD score	56.0 ± 12.1	76.1 ± 11.0	<0.0001
CLIF-SOFA score	7.1 ± 1.1	9.3 ± 1.8	<0.0001

ACLF Acute-on-chronic liver failure, *AD* Acute decompensation, *ALP* Alkaline phosphatase, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *BP* Blood pressure, *CLIF-C* Chronic liver failure consortium, *GGT* Gamma-glutamyl transferase, *ICU* Intensive care unit, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein, *NLR* Neutrophil-lymphocyte ratio, *MAP* Mean arterial pressure, *MELD* Model for end-stage liver disease, *Na* Sodium, *OF* Organ failure, *PaO2* Partial pressure of arterial oxygen, *SOFA* Sequential organ failure assessment, *WBCs* White blood cells

older than those in the study by Dihman et al., who reported a mean age of 46.0 ± 13.0 years [22].

In our study, HCV was the most common cause of chronic liver disease (57.8%). This is consistent with the fact that Egypt has the highest HCV prevalence in the world, which represents the main etiology of chronic liver disease among the Egyptian population [23]. This figure is higher than that reported by Moreau et al. (13% for HCV and 9% for HCV and alcohol) [1] and Dihman et al. (10% for HCV with alcohol) [22]. In both studies, alcohol was the main etiology of chronic liver

Table 4 Comparison between improved and deceased groups regarding categorical variables

	Improved (*n*=64)	Deceased (*n*=185)	*P*
Sex			
Males	47 (73)	130 (70.3)	0.678
Females	17 (27)	55 (29.7)	
Precipitating factor of ACLF			
Sepsis	16 (25)	108 (58.4)	<0.0001
Upper GI bleeding	7 (10.9)	18 (9.7)	
De novo AIH	1 (1.6)	0 (0)	
AIH flare	6 (9.4)	2 (1.1)	
DILI	7 (10.9)	2 (1.1)	
HBV	1 (1.6)	2 (1.1)	
HCV	0 (0)	1 (0.5)	
HDV	1 (1.6)	1 (0.5)	
HEV	0 (0)	2 (1.1)	
Wilson's disease	1 (1.6)	0 (0)	
Unknown	24 (37.5)	47 (25.4)	
Etiology of pre-existing CLD			
HCV	30 (46.8)	113 (61.1)	0.055
AIH	6 (9.4)	2 (1.1)	
Budd-Chiari syndrome	0 (0)	2 (1.1)	
HBV	5 (7.8)	8 (4.3)	
HBV-HCV co-infection	0 (0)	1 (0.5)	
Unknown	23 (35.9)	59 (31.9)	
Ascites			
No	37 (57.8)	38 (20.5)	<0.0001
Mild to moderate	24 (37.5)	131 (70.8)	
Marked	3 (4.7)	16 (8.6)	
Hepatic encephalopathy			
No	56 (87.5)	26 (14.1)	<0.0001
Grades I–II	7 (10.9)	116 (62.7)	
Grades III–IV	1 (1.6)	43 (23.2)	
Initial admission			
Ward	50 (78.1)	8 (4.3)	<0.0001
ICU	14 (21.9)	177 (95.7)	
Child-Pugh class			
B	16 (23.8)	3 (1.6)	<0.0001
C	48 (76.2)	182 (98.4)	
ACLF grade			
1	51 (79.7)	39 (21.1)	<0.0001
2	13 (20.3)	95 (51.4)	
3	0 (0)	51 (27.6)	

ACLF Acute-on-chronic liver failure, *AIH* Autoimmune hepatitis, *DILI* Drug-induced liver injury, *ICU* Intensive care unit, *GI* Gastrointestinal, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *HDV* Hepatitis D virus, *HEV* Hepatitis E virus

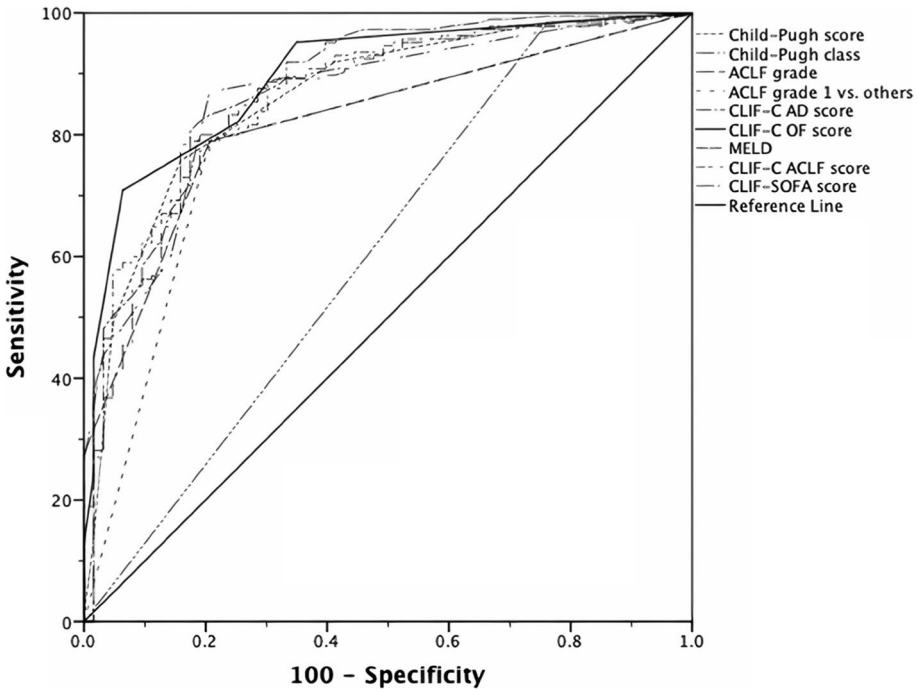

Fig. 2 ROC curves of the studied scores in prediction of in-hospital mortality. Legend: ACLF, acute-on-chronic liver failure; AD, acute decompensation; CI, confidence interval; CLIF-C, chronic liver failure consortium; MELD, model for end-stage liver disease; OF, organ failure; SOFA, Sequential Organ Failure Assessment

Table 5 Cox regression for the independent predictors of in-hospital mortality

	B	Wald	*P*	*OR*	95% *CI*
CLIF-C ACLF	0.04	22.54	<0.0001	3.25	1.03–10.25
Child-Pugh class (C vs. B)	1.18	4.06	0.044	1.04	1.02–1.06

ACLF Acute-on-chronic liver failure, *CI* Confidence interval, *CLIF-C* Chronic liver failure consortium, *OR* Odds ratio

disease (60.3% and 58%, respectively). Other identifiable etiologies of the pre-existing liver disease in our study came with variable degrees of agreement with others reported in the literature. Hepatitis B was similar (5.2%) to the Dihman et al. study (6%). Autoimmune hepatitis was higher in the Dihman et al. study (6%) compared to ours (3.6%). The etiology could not be identified in 32.1% patients in our study compared to 14% in the study by Dihman et al. However, cryptogenic cirrhosis is the second most common etiology in both studies. We believe that the high rate of unidentifiable etiology of the pre-existing cirrhosis in our study could be referred considerably to nonalcoholic fatty liver disease, an important condition for which we could not stand on a confirmed diagnosis at such a late stage of cirrhosis. Conclusively, these differences in the etiologic profile of cirrhosis in ACLF reflect the etiology of cirrhosis in the respective countries. Alcoholic cirrhosis constitutes 50–70% of all the underlying liver diseases of ACLF in the western countries, whereas viral hepatitis-related cirrhosis constitutes about 10–15% of all the cases [24–26]. However, in most of the Asian countries, HBV constitutes 70% and alcohol only about 15% of all the etiologies [27]. In contrast, HCV-related cirrhosis constitutes the majority in Egyptian patients [23].

In the same stream, the acute insult precipitating ACLF was variable among different studies. In our cohort, sepsis represented the most common precipitating factor (49.8%). We have no definite explanation for such a high rate. However, this might be attributed to the immune derangement commonly found in patients with advanced stages of cirrhosis, which makes them more prone to bacterial infections. Similarly, Dhiman et al. reported that bacterial infections represented 66% of the ACLF precipitating factors [22]. The CANONIC study reported a lower rate of bacterial infections (32.6%) [1]. It is to be noted that the APASL definition does not include infection/sepsis as the acute precipitating event of ACLF [28].

Acute GI bleeding represented the second most common precipitating factor in our study (9.2%). Negligence,

missing variceal screening programs, and/or non-adherence to portal pressure decompressing medications represented the main factors associated with acute variceal hemorrhage in this group of patients. Moreau et al. reported a comparable rate of variceal hemorrhage (13.2%) [1]. Meanwhile, Dhiman et al. reported a lower rate of 4% [22]. It is noteworthy that both studies reported a high proportion of active alcoholism (40% and 24.5%, respectively), which was not encountered in any of our studied patients. Dihman et al. also reported a higher incidence of autoimmune hepatitis flares (8%) compared to our rate of exacerbation (3.2%) and a higher rate of HEV (2%) compared to ours (0.4%) [22]. No precipitating factor could be identified in 30.9% of the patients in our study, which is lower than the figure reported by Moreau et al. (43.6%) [1].

Risk factors for mortality

The 28-day mortality in ACLF ranged between 30 and 40% [6]. The estimated global 90-day mortality was 58%, with some relative regional variations. South America had the highest rate (73%), followed by South Asia (68%) [29]. The reported mortality rate in our study was 74.3%. These variations might be attributed to the variance in the definition of ACLF and guidelines used in these different areas, the heterogeneity of patients' characteristics and ethnicities, and the relative variation in the reversibility of the acute precipitating insult besides the ACLF grade. Another important point that could influence the mortality rate is the availability of salvage liver transplantation for patients who develop progressive irreversible deterioration. The candidacy for liver transplantation becomes more sophisticated and perplexing when patients develop intractable sepsis, a relatively common condition that could contraindicate liver transplantation. In addition, liver transplantation would be declined for patients who develop kidney failure, the most common organ failure in ACLF, unless a combined liver-kidney transplant is available. Adding to that, most patients with advanced ACLF grade are not sufficiently stable to undergo liver transplantation. Indeed, all these factors collectively could influence the mortality rates among different studies and regions. Unfortunately, many of these factors have been reported in many of our patients, including intractable sepsis, advanced ACLF grade, donor unavailability, and improper conditions for receiving liver transplants. This could explain the higher mortality rate disclosed in our cohort.

In univariate analysis, the Child-Pugh score and class, CLIF-AD grades, and the MELD, CLIF-C AD, CLIF-C OF, CLIF-SOFA, and CLIF-ACLF scores were significantly worse in patients who were deceased at discharge.

Age significantly predicted mortality in our study as well as in five previous studies [30–34]. Albumin was significantly lower in the deceased group (2.3 vs. 2.7, $P<0.0001$). This is similar to the finding by Sun et al. (2.8 vs. 3.1 $P<0.001$) [34]. In our study, the white blood cell count was significantly higher in the deceased group (11.3 vs. 15.2, $P<0.0001$). The same was reported in the study by Sun et al.; survivors had a significantly lower WBCs count (6.7 vs. 8.1, $P=0.036$) [34]. We noted that platelets were significantly higher in the group of survivors. This finding was reported in four previous studies [34–37]. In the current study, INR was significantly lower in the group of survivors. This was also reported in four previous studies [34, 37–39]. It is noteworthy that although bilirubin is an important component of these scores, it did not show statistical significance between both groups. This finding was replicated in six previous studies [34–38, 40].

It is also to be noted that the total stay in ICU was significantly shorter in the deceased group (6.8 vs. 10.8, $P<0.0001$) and the total hospital stay was not statistically significant regarding mortality.

Multivariate analysis, using Cox regression, revealed that Child-Pugh (class C vs. B) and CLIF-C ACLF scores significantly and independently predict mortality. In the study by Jalan et al., CLIF-C ACLF was superior to MELD and Child-Pugh scores in predicting mortality in patients with ACLF in the validation database, with a higher c-statistics (0.744 vs. 0.645 vs. 0.653, respectively) [20]. We also found that the AUROC for the CLIF-C ACLF was larger than that of Child-Pugh and MELD scores (0.870 vs. 0.850 vs. 0.861, respectively). The Child-Pugh class had a smaller AUROC (0.611). When using Cox regression and including time to mortality, which adds to the accuracy of testing the discriminating ability, the CLIF-C ACLF had a higher odds ratio as compared to the Child-Pugh class C vs. B (3.25 vs. 1.04).

The limitations of the current study include that it was a single-center study. The high proportion of patients with HCV-related liver cirrhosis could hinder the generalization of the results. However, it adds to the spectrum of ACLF studies with other etiologies of chronic liver disease and strengthens the concept that cirrhosis is one of the baseline hallmarks of ACLF regardless of its etiology. In addition, the large sample size represents an important strength point.

Conclusions

In conclusion, all the liver-specific and ACLF-specific scores could significantly predict in-hospital mortality of patients with ACLF. However, CLIF-C ACLF and Child-Pugh class C were superior to other scores as they could significantly and independently predict in-hospital mortality.

Abbreviations
AASLD: American Association for the Study of Liver; ACLF: Acute-on-chronic liver failure; AD: Acute decompensation; AIH: Autoimmune hepatitis; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; ANA: Antinuclear antibody; APASL: Asian Pacific Association for the Study of Liver; ASMA: Anti-smooth muscle antibody; AST: Aspartate aminotransferase; AUC: Area under the ROC curve; BP: Blood pressure; CLD: Chronic liver disease; CLIF-C: Chronic liver failure consortium; CP: Child-Pugh; DILI: Drug-induced liver injury; EASL: European Association for the Study of Liver; FiO2: Fraction of inspired oxygen; GGT: Gamma-glutamyl transferase; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HDV: Hepatitis D virus; HEV: Hepatitis E virus; ICU: Intensive care unit; INR: International normalized ratio; LKM: Anti-liver kidney microsomal antibody; MAP: Mean arterial pressure; MELD: Model for end-stage liver disease; Na: Sodium; OF: Organ failure; PaO2: Partial pressure of arterial oxygen; ROC: Receiver operating characteristic curve; RUCAM: Roussel Uclaf Causality Assessment Method; SOFA: Sequential Organ Failure Assessment; WBCs: White blood cells; WGO: World Gastroenterology Organization.

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Authors' contributions
AW was the one who put the research idea. AM and ZT shared in the study design. SS and EM were assigned to data collection and processing. AW, AM, and ZT contributed in the data analysis and interpretation. EM and SS prepared the literature review. ZT wrote the manuscript. AW and AM revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the local Institutional Review Board of National Liver Institute, Menoufia University, Egypt. A signed written informed consent was obtained from all patients or their relatives before participation in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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