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Contents

Monthly Volume 14 Number 12 December 27, 2022

REVIEW

ORIGINAL ARTICLE

Basic Study

SYSTEMATIC REVIEWS

World Journal of Hepatology

Monthly Volume 14 Number 12 December 27, 2022

Contents

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SYSTEMATIC REVIEWS

CLIF-SOFA and CLIF-C scores for the prognostication of acute-on-chronic liver failure and acute decompensation of cirrhosis: A systematic review

Ebrahim Rashed, Jonathan Soldera

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Abstract

BACKGROUND

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by decompensation in individuals with chronic liver disease, generally secondary to one or more extra-hepatic organ failures, implying an elevated mortality rate. Acute decompensation (AD) is the term used for one or more significant consequences of liver disease in a short time and is the most common reason for hospital admission in cirrhotic patients. The European Association for the Study of Liver-Chronic-Liver Failure (EASL-CLIF) Group modified the intensive care Sequential Organ Failure Assessment score into CLIF-SOFA, which detects the presence of ACLF in patients with or without AD, classifying it into three grades.

AIM

To investigate the role of the EASL-CLIF definition for ACLF and the ability of CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD scores for prognosticating ACLF or AD.

METHODS

This study is a literature review using a standardized search method, conducted using the steps following the guidelines for reporting systematic reviews set out by the PRISMA statement. For specific keywords, relevant articles were found by searching PubMed, ScienceDirect, and BioMed Central-BMC. The databases were searched using the search terms by one reviewer, and a list of potentially eligible studies was generated based on the titles and abstracts screened. The data were then extracted and assessed on the basis of the Reference Citation Analysis (https://www.referencecitationanalysis.com/).

RESULTS

Most of the included studies used the EASL-CLIF definition for ACLF to identify cirrhotic patients with a significant risk of short-term mortality. The primary

outcome in all reviewed studies was mortality. Most of the study findings were based on an area under the receiver operating characteristic curve (AUROC) analysis, which revealed that CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD scores were preferable to other models predicting 28-d mortality. Their AUROC scores were higher and able to predict all-cause mortality at 90, 180, and 365 d. A total of 50 articles were included in this study, which found that the CLIF-SOFA, CLIF-C ACLF and CLIF-C AD scores in more than half of the articles were able to predict short-term and long-term mortality in patients with either ACLF or AD.

CONCLUSION

CLIF-SOFA score surpasses other models in predicting mortality in ACLF patients, especially in the short-term. CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD are accurate short-term and long-term mortality prognosticating scores.

Key Words: End-stage liver disease; Acute-on-chronic liver failure; CLIF-SOFA; CLIF-C ACLF; CLIF-C AD

Core Tip: Acute-on-chronic liver failure (ACLF) is a serious medical challenge worldwide, and its occurrence is a difficult clinical incident due to its severe presentation, quick disease course, and elevated short-term mortality. The European Association for the Study of Liver-Chronic-Liver Failure (EASL-CLIF) Consortium proposal has gained considerable acceptance as a diagnostic criteria for ACLF. CLIF-SOFA has increased the ability to detect patients with ACLF. Unless presenting with renal impairment and/or mild to moderate hepatic encephalopathy, cirrhotic patients with acute decompensation and single liver failure (or any other single "non-renal" organ failure) had a minimum mortality risk. These results suggest that CLIF-SOFA score surpasses other models in predicting mortality in ACLF patients, especially in the short-term.

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by liver decompensation in individuals with chronic liver disease. It is associated with one or more extra-hepatic organ failures and an elevated mortality rate[1-4].

Acute decompensation (AD) is the term used for the occurrence of one or more significant complications of liver disease in a short period of time (*i.e.*, bacterial infection, gastrointestinal haemorrhage, ascites, encephalopathy)[5-9]. It is the most common reason for hospital admission in cirrhotic patients. Most of these patients will develop AD without any other significant features, while others will develop AD associated with multiple organ failures (*i.e.*, kidney failure, declining liver function, and/or other organ failures). Nevertheless, AD patients with extra-hepatic organ failures are at greater risk for short-term mortality[10-12].

In Europe and America, the primary cause of ACLF is alcohol, while viral hepatitis infection is the main cause of ACLF in Asia, particularly in China[13]. Despite procedures such as haemodialysis and liver transplantation significantly increasing short-term survival, they are not widely available in medical care due to their high cost, the requirement for hospital admission, and the limited availability of liver resources[14]. ACLF places a significant financial burden on patients and on the healthcare system.

A European prospective multi-centric study named CANONIC developed and published in 2013 definitions and a classification and grading of ACLF. The most common reasons for cirrhosis were alcoholic liver disease, chronic hepatitis C, and/or both[15]. Hepatic (alcoholic liver injury) and extra-hepatic disorders (gastrointestinal bleeding or bacterial infection) were the most common precipitating disorders for decompensation of cirrhosis, with or without ACLF. The most common organ failures (OFs) were kidney (55.8% of ACLF patients) and liver failure (43.6%), then coagulation (27.7%) and cerebral failure (24.1%). Heart and respiratory failures were the least common, around 16.8% and 9.2%, respectively[15]. Twenty-eight-day transplant-free mortality rate in ACLF patients was 32.8%, while in

patients without ACLF, it was 1.9%[15].

Ascites, a higher model for end-stage liver disease (MELD) score, low haemoglobin (Hb) levels, and low mean arterial pressure were defined as predictive factors for ACLF development in a large single-centre Italian prospective cohort of cirrhotic outpatients[16]. The European Association for the Study of Liver-Chronic-Liver Failure (EASL-CLIF) consortium has stated that today's global mortality rate of ACLF ranges from 30% to 50%.

The aim of the current study is to provide an overview of research into the role of the EASL-CLIF definition for ACLF, as well as the ability of CLIF-Sequential Organ Failure Assessment (SOFA), CLIF-C ACLF and CLIF-C AD scores to predict adverse outcomes associated with chronic liver disease.

Prognostic scoring systems

Various predictive scores have previously been developed. Nearly fifty years ago, the Child-Turcotte-Pugh (CTP) (Table 1) score was established as the most relevant liver-specific score[17]. Wiesner's study evaluated data to develop the MELD score that outperformed the CTP score in predicting 90-d death in individuals with chronic end-stage liver disease[18]. The MELD-Na score (Table 2), which combines the MELD score with serum sodium content, has enhanced predictive accuracy in patients with cirrhosis awaiting liver transplantation[19]. The CLIF-SOFA score, a new scoring system that is an adaptation of the original SOFA score, was used to describe ACLF in the EASL-CLIF CANONIC study of ACLF in cirrhotic patients (Table 3). It has been used to distinguish AD from ACLF, classifying it into three grades[15]. The EASL-CLIF consortium also established the CLIF consortium organ failure (CLIF-C OF) score.

Jalan *et al*[20], described that age and white blood cell (WBC) counts are independent risk factors for death in subsequent investigations and developed the CLIF-C ACLF score. The EASL-CLIF Group created an online calculator for calculating CLIF-SOFA and either CLIF-C ACLF or CLIF-C AD (https://www.clifresearch.com/ToolsCalculators.aspx).

CLIF-C ACLF Score Formula: The CLIF-C ACLF Score Formula[21] combines (CLIF-C OF score, age, and WBC) with the following formula: CLIF-C ACLF = 10 × [0.33 × CLIF-OFs + 0.04 × Age + 0.63 × Ln (WBC)] – 2.

CLIF-C AD Score Formula: The CLIF-C AD Score Formula (non-ACLF patients with AD) combines (Age, Creatinine, international normalized ratio (INR), WBC, and Sodium) with the following formula [22,23]: CLIF-C AD = 10 × [0.03 × Age + 0.66 × Ln (Creatinine mg/dL) + 1.71 × Ln (INR) + 0.88 × Ln (WBC 10^9 cells/L) – 0.05 × (Sodium mmol/L) + 8].

ACLF Grades[15]: Grade I ACLF: Only kidney failure. [According to Shah *et al*[24], grade 1 could be with one of the following: Liver failure, kidney failure, coagulation, circulatory, or lung failure, with creatinine (1.5 - 1.9 mg/dL), or hepatic encephalopathy (grade 1 or 2), or brain failure with creatinine (1.5 - 1.9 mg/dL)]. Grade II ACLF: Two organ failures. Grade III ACLF: Three organ failures.

MATERIALS AND METHODS

This study is a literature review using a standardized search method, conducted using the steps following the guidelines for reporting systematic reviews set out by the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[25].

Search strategy

For relevant original studies, a literature search was conducted using PubMed, ScienceDirect, and BioMed Central-BMC databases. The search command used was a combination of words and Boolean characters: ("CLIF-SOFA" OR "CLIF-C ACLF" OR "CLIF-C AD") AND ("acute-on-chronic liver failure"). Reference Citation Analysis (https://www.referencecitationanalysis.com/) was used to supplement the search.

Study selection

Studies were included if they analyzed data of patients more than 18 years old from the emergency department or inpatient settings. They needed to report data using ACLF definitions and scores published by the EASL-CLIF group and had a full text available. Studies were excluded if they used only scores other than CLIF-SOFA and CLIF-C AD or CLIF-C ACLF, if they were not written in English or if they were reviews, letters, editorials, opinion articles, conference abstracts, and *in-vitro* studies.

Data extraction and synthesis

The databases were searched using the above search terms by one reviewer, and a list of potentially eligible studies was generated based on the titles and abstracts screened. Then, a full-text review was conducted, using the inclusion and exclusion criteria.

Table 1 Child-Turcotte-Pugh scores

Points	1	2	3
Ascites	Absent	Slight	Moderate
Serum Bilirubin (mg/dL)	< 2	2-3	> 3
Serum Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
PT ratio or	< 4	4-6	> 6
INR	< 1.7	1.7–2.3	> 2.3
HE	None	Grade I-II	Grade III-IV

PT: Prothrombin time; INR: International normalized ratio; HE: Hepatic encephalopathy.

Table 2 MELD and MELD-Na[62,63]: Model for end-stage liver disease–sodium

MELD	Mortality rate (%)	MELD-Na	Mortality rate (%) (90-d)
≤ 9	1.9	< 17	< 2
10-19	6	17-20	3-4
20-29	19.6	21-22	7-10
30-39	52.6	23-26	14-15
≥ 40	71.3	27-31	27-32
		≥ 32	65-66

MELD: End-stage liver disease.

Table 3 CLIF-SOFA score[64]

Points	0	1	2
Liver Bilirubin (mg/dL)	< 1.2	≥ 1.2 - < 2.0	≥ 2.0 - < 6.0
Renal Creatinine (mg/dL)	< 1.2	≥ 1.2 - < 2.0	≥ 2.0 - < 3.5
Neurological HE grade	-	1	2
Haematological INR	< 1.1	≥ 1.1 - < 1.25	≥ 1.25 - < 1.5
Circulation MAP (mmHg)	≥ 70	< 70	Dopamine ≤ 5 or Dobutamine or Terlipressin
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	> 400; > 512	> 300-≤ 400; > 357 - ≤ 512	> 200 - ≤ 300; > 214 - ≤ 357

RRT: Renal Replacement Therapy; HE: Hepatic encephalopathy; INR: International Normalized Ratio; PaO_2: Partial pressure of arterial oxygen; MAP: Mean Arterial Pressure; FiO_2: Fraction of inspired oxygen; SpO_2: Pulse oximetric saturation.

RESULTS

Study selection

Figure 1 shows the study search and the selection process, including the reasons for exclusion after a full-text review. A total of 50 related articles were included in the final review.

Study quality

Most of the included studies used the EASL-CLIF definition for ACLF to identify patients with cirrhosis who had a significant risk of short-term mortality. Some articles used the Asian Pacific Association for the Study of the Liver and Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH-ACLF) prognostic criteria. The included studies were not assessed using a quality assessment tool, although they were considered to be good quality.

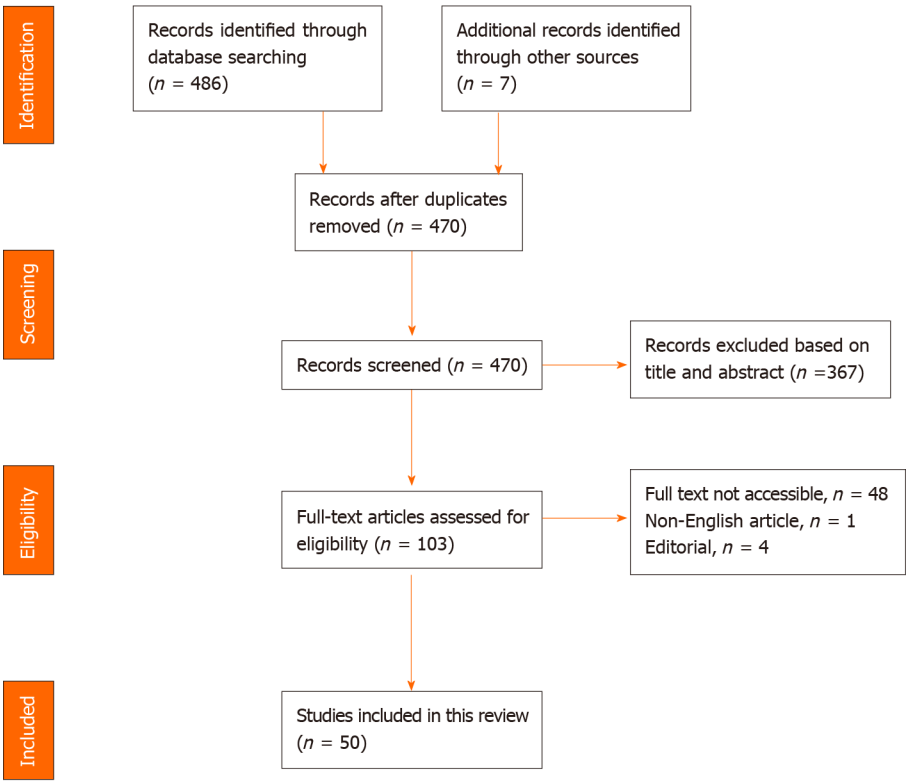

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Figure 1 PRISMA diagram of the study selection process.

Study outcome

The primary outcome in all reviewed studies was mortality. Most of the studies' findings were based on an area under the receiver operating characteristic curve (AUROC) analysis, which revealed that CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD scores were preferable to other models predicting 28-d mortality (Table 4). They had the greatest AUROC scores predicting overall mortality at 90, 180, and 365 d.

DISCUSSION

ACLF has become a serious medical challenge, and it remains a complex clinical scenario for hepatologists and specialists in different related departments due to its severe presentation, and quick disease course with high short-term mortality. Regional differences when defining ACLF and understanding its diagnostic methods has led to many clinical phenotypes. The current therapeutic management of ACLF patients primarily focuses on treating and supporting multiple organ failures[26].

The CANONIC study introduced accurate criteria for the diagnosis of this condition. The CLIF-SOFA score was developed and evaluated for the prognosis of ACLF in the CANONIC research[15]. This development has increased the ability to distinguish patients with ACLF from those with AD using the CLIF-SOFA parameters[15].

Every scoring system has advantages and disadvantages. Even though the CLIF-SOFA score has a significant prognosticative accuracy, its calculation is challenging due to the combination of many indicators[14]. The CTP score is calculated by the ascites, serum bilirubin, albumin, prothrombin time, and hepatic encephalopathy (HE) levels[17]. The presence of HE and ascites is a component of the CTP score; nevertheless, these are subjective, without a defined cut-off value. The MELD score includes three laboratory markers: INR, bilirubin, and creatinine; nevertheless, it is susceptible to confounding factors such as haemorrhage, ascites, and diuretic treatment, and there are no obviously defined cut-off levels for identifying patients with cirrhosis[27]. The MELD score does not include subjective indicators, which may diminish evaluating reliability[28].

Hyponatraemia is strongly associated with the prognosis of cirrhotic patients, especially those with ascites; thus, the MELD-Na score was developed to improve on the MELD score[29].

Jalan *et al*[20] in 2014, showed that the CLIF-C OF accuracy is similar to the CLIF-SOFA score in predicting mortality. The CLIF-C ACLF score does not consider only the role of extra-hepatic organ injuries, circulatory system failure, and coagulation impairment on prognosis, but also includes the WBC count, in order to assess the level of inflammation. In this study, the CLIF-C ACLF score outper-

Table 4 Summary of selected studies

Ref.	Year	Country	Aim	Setting	Results	Conclusions
Kuo *et al*[65]	2021	Taiwan	Assess the predictive value and clinical reliability of three different scores	ACLF patients admitted to the ICU	Non-survivor: CLIF-C ACLF, CLIF-C ACLF lactate, and CLIF-C ACLF-D were 58.85 ± 11.40, 60.88 ± 13.71, and 34.03 ± 1.57, respectively. Survivor: 44.55 ± 9.14, 46.91 ± 11.66, and 32.29 ± 1.17, respectively, (all *P* values < 0.01)	The CLIF-C ACLF-D score may be a better predictor of short- and long-term mortality
Li *et al*[66]	2017	China	Assess various prognostic scores, such as the CLIF-C OFs, CLIF-SOFAs, CLIF-C ACLFs, ACLF grade, and MELD, predicted short-term (28-d) mortality	CHB patients with ACLF	Scores in no ACLF group and for ACLF group grades 1, 2, and 3, respectively: CLIF-C OFs: 7, 9, 10, and 13; CLIF-C ACLFs: 29, 37, 44, and 60; CLIF-SOFAs: 5, 7, 9, and 13; MELDs: 16, 22, 30, and 37	CLIF-C OF score outperforms other scores
Dong *et al*[67]	2020	China	Determine the characteristics and outcomes of ACLF	ACLF patients who have or do not have cirrhosis	COSSH ACLF score (AUROC = 0.778 or 0.792, 95%CI 0.706-0.839 or 0.721–0.851) displayed the better prognostic ability for EASL ACLF patients with non-cirrhosis. CLIF-C ACLF score (AUROC = 0.757 or 0.796, 95%CI 0.701–0.807 or 0.743-0.843) still was the best prognostic scoring system in EASL ACLF patients with cirrhosis	CLIF-C ACLF score was better at predicting short-term mortality in ACLF patients with cirrhosis, while the COSSH ACLF score was better for ACLF patients without cirrhosis
Grochot *et al*[68]	2020	Brazil	Determine the accuracy of the presence of ACLF in predicting mortality.	Patients with cirrhosis	CLIF-SOFA score at 28-, 90-, and 365-d was 1.32, 1.3, and 1.2, respectively. CLIF-C AD/ACLF score was 1.0, 1.0, and 1.0, respectively	CLIF-SOFA score increased mortality by 1.3 times for each point
Jacques *et al*[41]	2020	Brazil	Assess and compare the liver-specific scores ability to predict mortality	Cirrhotic patients with SBP	CLIF-SOFA was able to predict mortality at 30-, 90-, and 365-d, with an AUROC of 0.75, 0.64, and 0.64, respectively. CLIF-C AD or CLIF ACLF scores 0.59, 0.51, and 0.52, respectively	CLIF-SOFA outperformed other liver-specific measures
Terres *et al*[39]	2022	Brazil	Assess and compare the significance of liver-specific scores in predicting mortality	HRS patients who received terlipressin	CTP at 30-, 90- and 365-d mortality 0.76, 0.75 and 0.72, respectively. CLIF-SOFA 0.66, 0.63, and 0.57. CLIF-C ACLF 0.60, 0.55, and 0.53. MELD 0.67, 0.64, and 0.5. MELD-Na 0.65, 0.63, and 0.52	CTP was able to predict increased mortality at 30-, 90- and 365-d
Terres *et al*[40]	2021	Brazil	Evaluate the liver-specific scores to predict mortality	AOVH patients who received terlipressin	AUROC at 30- and 90-d**:** MELD-Na 0.77 and 0.78. CLIF-SOFA 0.76 and 0.75. CLIF-C AD or ACLF 0.64 and 0.60. MELD 0.75 and 0.77. CTP 0.75 and 0.76	CLIF-SOFA was better in ACLF patients. CTP performed better in AD patients
Grochot *et al*[56]	2019	Brazil	Assess the validity of CLIF SOFA in predicting mortality and compare it to other liver-specific scores	AD and ACLF patients	AUROC **at** 28-, 90- and 365-d**,** respectively: CLIF-SOFA 0.71, 0.75 and 0.66. CLIF-C AD/ACLF 0.52, 0.51, and 0.56. MELD 0.54, 0.50, and 0.52. MELD-Na 0.57, 0.54, and 0.55	CLIF-SOFA predicted 90-d mortality better than other scores
Jacques *et al*[69]	2021	Brazil	Evaluate the relation between ACLF and mortality	Cirrhotic patients with SBP	Scores for 28- and 90-d mortality, respectively: MELD 0.83 and 0.87. CLIF-SOFA 1.1 and 1.1. CTP 31 and 8.3	Elevated CLIF-SOFA scores and the presence of ACLF were related to higher 28- and 90-d mortality
Engelmann *et al*[21]	2018	United Kingdom	Assess if the currently available scores can identify patients with ACLF	Patients with ACLF	AUROC of 28-d mortality prediction: CLIF-C ACLF 0.8. CLIF-C OF 0.75. MELD, 0.68. CP 0.66	CLIF-C ACLF accurately predicted 28-d mortality
Barosa *et al*[70]	2017	Portugal	Evaluate CLIF-C ACLF, MELD, MELD-Na, and CTP scores for short/medium-term mortality, to identify ACLF frequency and to compare mortality between non-ACLF and ACLF patients	Patients admitted for AD of cirrhosis	Cut-off point in 28- and 90-d mortality, respectively: CLIF-C ACLF 50 and 50. CTP 10 and 10. MELD 17 and 14. MELD-Na 22 and 22	CLIF-C ACLF score outperformed other scores
Ferreira Cardoso *et al*[71]	2019	Portugal	Validate the EASL-CLIF C scores	Patients with and without ACLF	AUROC for CLIF-C ACLF score for 28-d mortality was (0.856 ± 0.071)	CLIF-C AD score of 60 was related to an increased risk of

						developing ACLF
Maipang *et al*[57]	2019	Thailand	Assess ACLF prognostic models and investigation of their discriminative capacities in ACLF patients	Cirrhotic patients with AD and ACLF	Scores for 28-d, 90-d, 6-mo, and 1-yr mortality, respectively: CLIF-SOFA: 0.84, 0.85, 0.80, 0.80. CLIF-C OF: 0.83, 0.82, 0.78, and 0.78. CLIF-C ACLF: 0.79, 0.80, 0.77, and 0.77. CTP: 0.7, 0.67, 0.64, and 0.63. MELD: 0.63, 0.60, 0.56, and 0.56. MELD-Na: 0.63, 0.59, 0.56, and 0.56. iMELD: 0.73, 0.71, 0.67, and 0.68. APACHE II: 0.69, 0.65, 0.63, and 0.63	The CLIF-SOFA had similar predictive accuracy for 28-d mortality as the CLIF-C OF
Li *et al*[36]	2016	China	Assess if CLIF-C OFs criteria can be used to identify patients and if the CLIF-C ACLF score can be used to predict prognosis	HBV cirrhotic patients with ACLF	Assess patients with ACLF for 28-, 90-, 180-, and 360-d mortality, respectively: HBV-ACLF: 0.654, 0.645, 0.644, and 0.640. CLIF-C ACLF: 0.704, 0.685, 0.687, and 0.682. MELD: 0.554, 0.543, 0.543, and 0.540. MELD-Na: 0.549, 0.541, 0.541, and 0.537. Patients without ACLF: for 28-, 90-, 180-, and 360-d mortality, respectively: HBV-AD: 0.737, 0.716, 0.720, and 0.721. CLIF-C AD: 0.733, 0.724, 0.728, and 0.728. MELD: 0.667, 0.653, 0.657, and 0.639. MELD-Na: 0.719, 0.710, 0.701, and 0.682	CLIF-C ACLFs were found to be more accurate in predicting short-term mortality
Chirapongsathorn *et al*[49]	2022	Thailand	Collect epidemiological data and assess a scoring system for predicting mortality	ACLF patients.	AUROC of prognostic scores for 30- and 90-d mortality, respectively: CLIF-SOFA: 0.64 and 0.61 (95%CI: 0.585-0.704). CLIF-OF: 0.62 and 0.59. CLIF-C: 0.62 and 0.61. MELD: 0.60 and 0.56. MELD-Na: 0.60 and 0.57	CLIF-SOFA score had a higher AUROC than the other scores
Zhang *et al*[31]	2018	China	Assess bacterial infection and predictors of mortality	ACLF patients with autoimmune liver disease	CLIF-SOFA score for 28-d mortality was 1.362 and 1.093, respectively.Scores for 90-d mortality were, respectively: CLIF-SOFA 2.936 and 1.578. MELD 1.232 and 0.664. CP 2.003 and 0.595	All scores of ACLF patients with bacterial infection were high
Shin *et al*[72]	2020	South Korea	To look into the risk factors for mortality in cirrhotic patients and to see how ACLF affected their prognosis	Cirrhotic patients with variceal bleeding	Prediction of mortality at 28- and 90-d with AUROC were, respectively: CTP 0.842 and 0.846. MELD 0.857 and 0.867. MELD-Na 0.828 and 0.834. CLIF-SOFA 0.895 (95%CI, 0.829-0.962) and 0.897 (95%CI, 0.842-0.951)	CLIF-SOFA model well predicted 28-d or 90-d mortality
Gao *et al*[73]	2018	China	Investigate the CLIF-SOFA lung score's predictive value and determine the best voriconazole regimen	ACLF patients with IPA	CLIF-SOFA 10 (P = 0.083). CLIF-C ACLF 46.8 (P = 0.028). MELD 27.2 (P = 0.145). MELD-Na 28.6 (P = 0.064)	Patients with a CLIF-SOFA lung score of less than 2 had a superior 28-d survival rate than those with a lung score of more than 1 (P = 0.001)
Chen *et al*[74]	2021	China	Create a predictive nomogram	HBV-ACLF patients undergoing LT	CP score (0.626), MELD (0.627), MELD-Na (0.583), CLIF-C OF (0.674), and CLIF-C ACLF (0.684)	The nomogram's concordance index for predicting 1-yr survival was 0.707, which was significantly greater than that of other prognostic models. The nomogram could be helpful in determining which HBV-ACLF patients may improve after LT
Yu *et al*[75]	2021	China	Multicenter study to develop and evaluate a novel scoring system that uses baseline and dynamic data to predict short-term prognosis	ACLF patients	For 90-d prognosis: DP-ACLF with an AUC value of 0.907, CTP (0.601/74.6%), MELD (0.721/76.2%), MELD-Na (0.740/73.8%), CLIF-SOFA (0.701/76.9%), CLIF-C ACLF (0.694/74.6%), and COSSH-ACLF (0.724/77.7%) (P < 0.001)	The validation group had a higher predictive accuracy of DP-ACLF on ACLF prognosis and an accuracy rate of 85.4%, according to ROC analysis
Liu *et al*[35]	2020	China	Assess different prognostic models to predict short-term mortality	ACLF patients	The AUROCS of the CLIF-SOFA score, PWR, ALBI score, and MELD score was 0.804, 0.759, 0.710, and 0.670, respectively	CLIF-SOFA was the best model for predicting 28-d mortality
Zhang *et al*[76]	2015	China	Examine and contrast the various ACLF diagnostic criteria currently in use. Also,	Selected patients were cirrhotic, fulfilling at	CTP 12 and 11 (P = 0.53). MELD 17.8 and 16.0 (P = 0.02). MELD-Na 20.1 and 18.7 (P = 0.02). CLIF-SOFA 7 and 7 (P = 0.01)	The maximum rise in the CLIF-SOFA score, MELD-Na score, and total bilirubin were all

			to identify predictors of the progress from ACLF at enrolment defined by APASL alone or by both APASL and CMA	least APASL criteria for ACLF		independent predictors of progression into post-enrollment EASL-CLIF ACLF from ACLF at enrollment
Li *et al*[77]	2020	China	Randomized study to assess the scoring systems for predicting short-term results	HBV-ACLF patients	ALBI score (30-d mortality: HR = 3.452; 90-d mortality: HR = 3.822), MELD (30-d mortality: HR = 1.073; 90-d mortality: HR = 1.082), CLIF-C ACLF score (30-d mortality: HR = 1.061; 90-d mortality: HR = 1.065)	All scores accurately predicted 30-d and 90-d mortality. A higher CLIF-C ACLF score was linked to a lower overall survival rate
Zhang *et al*[14]	2020	China	Find prognostic scores that can be used to predict short- and long-term outcomes	ACLF patients with cirrhosis	Scores for survivors and [non-survivors] at 28-d, 3- and 6-mo, respectively: CTP 10 [12] (P = 0.001), 10 [11] (P = 0.028) and 10 [11] (P = 0.033). MELD 16 [24] (P = 0.004), 15 [23] (P = 0.001) and 15 [23] (p=0.002). MELD-Na 18 [24] (P = 0.081), 16.54 [23.27] (P = 0.011) and 17.27 [23] (P = 0.020). CLIF-C OF 9 [11] (P = < 0.001), 9 [10.00] (P = 0.001) and 9 [10] (P = 0.001). CLIF-SOFA 8 [12] (P ≤ 0.001), 8.55 [11.46] (P ≤ 0.001) and 8.53 [11.33] (P ≤ 0.001). CLIF-C ACLF 45.01 [53.98] (P ≤ 0.001), 44.39 [52.85] (P ≤ 0.001) and 44.11 [52.56] (P = 0.001)	The CLIF-SOFA score was particularly useful for assessing 28-d mortality
Kim *et al*[42]	2016	South Korea	A comparative study to evaluate the performance of suggested ACLF-specific scores in predicting short-term mortality	Alcoholic hepatitis patients	The AUROC of CLIF-SOFA, CLIF-C OFs, DF, ABIC, GAHS, MELD, and MELD-Na was 0.86 (0.81-0.90), 0.89 (0.84-0.92), 0.79 (0.74-0.84), 0.78 (0.72-0.83), 0.81 (0.76-0.86), 0.83 (0.78-0.88), and 0.83 (0.78-0.88), respectively, for 28-d mortality. CLIF-SOFA score of 8 had (78.1% Sn and 79.7% Sp), and CLIF-C OFs of 10 had (68.8% Sn and 91.4% Sp) for predicting 28-d mortality	CLIF-SOFA and CLIF-C OF scores performed well for short-term mortality
Costa E Silva *et al*[78]	2021	Brazil	Assess how well prognostic scores predict mortality	Cirrhotic patients admitted to the ICU	AUC revealed in all patients: CTP 0.701, APACHE II 0.695, MELD 0.727, MELD-Na 0.729, MESO index 0.723, iMELD 0.640, SOFA 0.753, CLIF-SOFA 0.776, CLIF-C OF 0.807 and CCI 0.627. CLIF-C OF in ACLF patients (0.749). CLIF-SOFA in AD patients (0.716) and CLIF-C AD (0.695)	CLIF-C OF and CLIF-SOFA had the best ability to predict mortality in all patients
Chen *et al*[38]	2020	Taiwan	Compare the eight prognostic scores	Cirrhotic patients with ACLF	Score on admission to ICU median (IQR) (P ≤ 0.001): CTP 9.0, MELD 23.0, CLIF-C OF 10.0, CLIF-C ACLF 49.2, SAP III 51.0, MPM0-III 0.0 (P = 0.001), APACHE II 16.0, and APACHE III 81.0. Predict overall mortality by AUROC: CTP 0.719, MELD 0.702, CLIF-C OF 0.721, CLIF-C ACLF 0.772, MPM0-III 0.607, SAP III 0.739, APACHE II 0.756 and APACHE III 0.817	APACHE III and CLIF-C ACLF scores were superior to other models for predicting overall mortality
Sheng *et al*[79]	2021	China	Create a new and effective prognosis model and identify new prognostic factors	HRS with AD patients	AUROC in derivation and validation, respectively: GIMNS (0.830 and 0.732), MELD (0.759 and 0.623), CLIF-SOFA (0.767 and 0.661), COSSH-ACLF (0.759 and 0.674). Mortality at 28-d according to the developed GIMNS score: (GIMNS ≥ 2) 100.0%, (GIMNS 1-2) 73.8%, (GIMNS 0-1) 57.1% and (GIMNS < 0) 30.3%	GIMNS had a higher accuracy AUROC and outperformed MELD and CLIF-SOFA
Hong *et al*[80]	2016	South Korea	Evaluate the features and outcomes of ACLF patients	ACLF patients with underlying liver disease	Scores in Type A (non-cirrhosis), B (cirrhosis), and C (cirrhosis with the previous decompensation), respectively: MELD 29, 27 and 26. Hepatic CLIF-SOFA 19, 34 and 21. Extra-hepatic CLIF-SOFA 7, 11 and 31	The 30-d overall survival rate for types A, B, and C, respectively, was 85.3%, 81.1%, and 83.7%
Sy *et al*[54]	2016	Canada	Assess if the CLIF-SOFA score could predict survival	Severely ill patients with ACLF	APACHE II 23; MELD 26; CTP 12; SOFA 15 and CLIF-SOFA 17. The CLIF-SOFA (AUROC 0.865). SOFA (AUROC 0.935)	CLIF-SOFA outperformed the other scores
Cai *et al*[2]	2019	China	Evaluate prognostic scoring models and create prediction models	Various causes of AD in cirrhotic patients	Hepatitis B group, AUROC for 28-d mortality for MELD, CLIF-C-AD, MELD-Na, AARC-ACLF, and the newly developed AD scores was 0.663, 0.673, 0.657, 0.662, and 0.773, respectively.	In predicting the prognosis of AD cirrhosis, the newly developed scoring models for short-term

					Alcoholic liver disease group, 0.731, 0.737, 0.735, 0.689, and 0.778, respectively. Others group 0.765, 0.767, 0.814, 0.720, and 0.814, respectively	mortality outperformed the other models
Marciano *et al*[81]	2017	Argentina	Compare the predictive accuracy for 28- and 90-d transplant-free mortality of a modified CLIF-SOFA score with that of the classic CLIF-SOFA and KDIGO scores	AKI in cirrhotic patients with AD	Classic CLIF-SOFA and modified CLIF-SOFA by AUCROC: In 28-d transplant-free, 0.93 and 0.92 (P = 0.34), respectively. In 90-d transplant-free, 0.79 and 0.78 (P = 0.78), respectively. In AKI 28-d and 90-d transplant-free mortality by AUCROC, 0.67 (P = 0.002) and 0.63 (P = 0.02)	Both CLIF-SOFA scores were extremely accurate in predicting 28-d and 90-d transplant-free mortality
Xu *et al*[82]	2018	China	Recognizing mortality risk variables and optimizing stratification are crucial for increasing survival rates	Cirrhotic patients with pneumonia	Scores by AUROC for predicting mortality in 30-d and 90-d respectively: CLIF-SOFA 0.890 and 0.900. MELD 0.853 and 0.889. MELD-Na 0.801 and 0.849, qSOFA 0.854 and 0.777, PSI 0.867 and 0.831. CTP 0.726 and 0.768	CLIF-SOFA outperformed the other models in predicting mortality
Silva *et al*[83]	2021	Brazil	Assess the prognostic scores predicting mortality	Cirrhotic patients who were admitted to the ICU without being pre-screened	ROC curves SOFA 0.88, MELD-Na 0.76, MELD 0.75, CPS 0.71 and SAPS 3 (0.51). In patients with ACLF, CLIF-ACLF 0.74, CLIF-OF 0.70, MELD-Na 0.73 and MELD 0.69, SAPS 3 (0.55), SOFA 0.63 and CLIF-SOFA 0.66	In patients with and without ACLF, CLIF-ACLF and SOFA had higher accuracy in predicting mortality
McPhail *et al*[46]	2015	United Kingdom	Compare the capabilities of SOFA and CLIF-SOFA scores to predict patient survival and evaluate CLIF-SOFA	Cirrhotic patients	At the time of admission, with AUROC values, CLIF-SOFA and SOFA scores were 0.813 and 0.799, respectively. At 48 h after admission were 0.853 and 0.840, respectively. After 1 wk were 0.842 and 0.844, respectively	SOFA and CLIF-SOFA scores appear to have equal ability to predict patient survival
Yang *et al*[52]	2022	China	Estimate the short-term prognosis of ACLF patients	ACLF patients who had undergone LT	AUROC of MELDs 0.704, ABIC: 0.607, CLIF-C OFs 0.606, CLIF-C ACLFs 0.653 and CLIF-SOFAs 0.633 of the 90-d outcome	MELDs had a higher AUROC than others for predicting the 90-d outcome in ACLF patients after LT
Moreau *et al*[15]	2013	12 European countries	Multicenter study to establish ACLF diagnostic criteria and characterize the progression of the disease	Cirrhotic patients with AD	The increased 28-d mortality rate was linked to three risk variables identified from the CLIF-SOFA score at enrollment: ≥ 2 organ failures, kidney failure alone, a combination of renal dysfunction, and a single organ failure other than kidney and/or hepatic encephalopathy (mild-moderate)	In patients with ACLF, higher CLIF-SOFA scores and leukocyte counts were predictors of mortality. The mortality rates at 28-d and 90-d, respectively: No ACLF 4.7% and 14%. ACLF g1: 22.1% and 40.7%. ACLF g2: 32% and 52.3%. ACLF g3: 76.7% and 79.1%
Li *et al*[37]	2021	China	Create a new simple prognostic score that can accurately predict outcomes	HBV-ACLF patients	The C-indices of the new score for 28- and 90-d mortality (0.826 and 0.809), COSSH-ACLF 0.793 and 0.784; CLIF-C ACLF 0.792 and 0.770; MELD 0.731 and 0.727; MELD-Na 0.730 and 0.726 (all P < 0.05)	The C-indices of the new score were significantly higher than other existing scores for 28-d and 90-d mortality
Perdigoto *et al*[58]	2019		Identify and characterize ACLF, and compare the CLIF-C OF score to the MELD-Na and the CP score. Also, to assess the CLIF-C ACLF and CLIF-C AD scores	Patients with ACLF	In the whole study group, the AUC: For 28-d mortality, the scores MELD, CLIF-C OF, and CP were 0.908, 0.844, and 0.753, respectively. For 90-d mortality 0.902, 0.814, and 0.724, respectively (P < 0.0001 for AUC in all scores)	CLIF-C OF shows good accuracy and diagnoses ACLF. MELD performed better in terms of 90-d mortality prediction
Ramzan *et al*[84]	2020		Evaluate the CLIF-C CLF score and compare it to the MELD score	ACLF patients in ICU	MELD scores 30, 40 and 50 at 48 h were 0.532, 0.594 and 0.529, respectively. CLIF-C ACLF ≥ 70 at 0 h, 24 h, and 48 h were 0.498, 0.605, and 0.643, respectively	CLIF-C ACLF score of 70 or higher accurately predicts mortality
Verma *et al*[85]	2021		Assess the prognostic models	ACLF patients	Day-7 AARC model had the numerically highest c-index, 0.872, best accuracy of 84.0%, Day-7 NACSELD-ACLF sensitivity (100%) but with a lower PPV (70%) for mortality	Patients having an AARC score of > 12 on day 7 had the lowest 30-d survival rate. All model performance parameters were better on day 7
Picon *et al*[59]	2017	Brazil	Assess prognostic	Patients with	Patients with ACLF, at 28-d from the	The CLIF-C ACLF score

			scores	AD of cirrhosis and ACLF	diagnosis: CLIF-C ACLF with an AUC of 0.71. Patients with AD, regarding 28-d mortality: CLIF-C AD 0.75; CP 0.72; MELD 0.75; MELD-Na 0.76; CLIF-C OF 0.74. Patients with AD regarding 90-d mortality: CLIF-C AD 0.70; CP 0.73; MELD 0.7; MELD-Na 0.73; CLIF-C OF 0.65	is the most accurate for predicting 28-d death in patients with ACLF. The CLIF-C AD score was also good in predicting death in cirrhosis with AD
Gupta *et al*[44]	2017	India	Assess the variations in mortality outcomes and predictors	Patients admitted with AD and ACLF caused by hepatic or extra-hepatic insults	AUROC for 28-d mortality in the extrahepatic ACLF group for CLIF-SOFA, MELD, iMELD, APACHE-11, and CTP was 0.788, 0.724, 0.718, 0.634, and 0.726, respectively. AUROC for 28-d mortality in the hepatic ACLF group for CLIF-SOFA, MELD, iMELD, APACHE-11, and CTP was 0.786, 0.625, 0.802, 0.761, and 0.648, respectively	iMELD and CLIF-SOFA were the best for predicting 28-d mortality
Niewiński *et al*[45]	2020	Poland	Use the available prognostic scores to find the best mortality risk factor(s)	Critically unwell ACLF patients	Predictive 90-d mortality: MELD 1.10, SOFA 1.33, CLIF-SOFA 1.40, and CLIF-C OF 1.64	SOFA score surpassed the CLIF-C values
Kulkarni *et al*[55]	2018	India	Determine the in-hospital predictors of 28-d mortality	ACLF patients admitted to the Medical ICU	MELD 0.783 (Sn 75% and Sp 82.1%). CLIF-SOFA 0.947 (Sn 83.3% and Sp 96.4%). CTP 0.795 (Sn 94.4% and Sp 57.1%). APACHE-II 0.876 (Sn 91.6% and Sp 78.5%)	CLIF-SOFA and APACHE-II scores had a superior ability to predict mortality
Dhiman *et al*[86]	2014	India	Assess the efficacy of the CLIF-SOFA and APASL definitions of ACLF in predicting the short-term prognosis of ACLF patients	Patients selected were cirrhotic with AD	AUROCs for 28-d mortality were 0.795, 0.787, 0.739, and 0.710 for CLIF-SOFA, APACHE-II, CTP, and MELD, respectively	The strongest predictor of short-term mortality was the CLIF-SOFA score
Safi *et al*[87]	2018	Germany	Evaluate how infection detected at the time of admission, as well as other clinical baseline factors, affected the mortality	Cirrhotic patients with emergency admissions	Predictors of mortality up to 90 d (all patients): HR, 95%Cl, and *P*, respectively: SOFA 0.15, 0.03-0.69 and 0.015. CLIF C ACLF 1.09, 1.06-1.13 and < 0.001. Infection and CLIF-SOFA and infection and CLIF-C-ACLF: HR, 95%CI and *P*, respectively: CLIF-SOFA 1.33, 1.17- 1.51 and < 0.001 CLIF-SOFA: Infection 0.85, 0.71-1.02 and 0.074. CLIF-C-ACLF 1.09, 1.06-1.12 and < 0.001 CLIF-C-ACLF: Infection 0.96, 0.92-1.01 and 0.082	Infection reduced the significant relation between mortality and CLIF-C-ACLF or CLIF-SOFA-score
Leão *et al*[88]	2019	Brazil	Assess how different ACLF diagnostic criteria performed in terms of predicting mortality	Cirrhotic patients with AD	AUROC at 28-d for CLIF-C, AARC and NACSELD criteria were 0.710, 0.560 and 0.561 ($P = 0.002$), respectively. AUROC at 90-d mortality were 0.760, 0.554 and 0.555 respectively ($P < 0.001$)	CLIF-C performed better in predicting mortality at 28-d and 90-d
Bartoletti *et al*[89]	2018	Different European countries	Summarize the current epidemiology of BSI, and assess predictors of 30-d mortality and antibiotic resistance risk factors	Cirrhotic patients	In a Cox regression model, CLIF-SOFA scores were (HR 1.35; 95%CI 1.28-1.43; $P < 0.001$)	The SOFA and CLIF-SOFA scores were the best predictors of 30-d mortality
Mendizabal *et al*[47]	2021	11 Latin American countries	Evaluate whether SARS-CoV-2 infection affects the outcome and assess the effectiveness of the different prognostic models in predicting mortality	Hospitalized cirrhotic patients	AUROC for performance evaluation in predicting 28-d mortality for CLIF-C, NACSELD, CTP score and MELD-Na were 0.85, 0.75, 0.69, 0.67; respectively ($P < 0.0001$)	In patients with cirrhosis and SARS-CoV-2 infection, CLIF-C performed better than other models

ACLF: Acute-on-chronic liver failure; AD: Acute decompensation; AUC: Area under the curve; AOVH: Acute oesophageal variceal haemorrhage; HRS: Hepatorenal syndrome; CTP: Child-Turcotte-Pugh; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MELD: Model of End-Stage Liver Disease; iMELD: integrated MELD; MELD-Na: sodium MELD; CPC: Child-Pugh class; SOFA: Sequential Organ Failure Assessment; CLIF-SOFA: CLIF-Consortium modification of Sequential Organ Failure Assessment; CLIF-C OF: Organ Failure score; ICU: Intensive care unit; CHB: Chronic hepatitis B; IPA: Invasive pulmonary aspergillosis; CMA: Cow milk induced allergies; APASL: Asian Pacific Association for the Study of the Liver; CPS: Complex Problem Solving; LT: Liver transplantation; PPV: Pulse pressure variation; BSI: Bronchiectasis severity index.

formed the CTP, MELD and MELD-Na scores[30].

This was also true of the CANONIC study data, which demonstrated that CLIF-SOFA, CLIF-C OF and CLIF-C ACLF scores were able to outperform CTP, MELD, and MELD-Na scores when predicting short- and long-term mortality in ACLF patients[15,20].

ACLF and infection

Zhang *et al*[31] in 2018, assessed the relationship between bacterial infection and predictors of mortality in ACLF patients with autoimmune liver disease. No significant association was found between 28-d and 90-d transplant-free mortality and any predictor. The CTP, MELD, and CLIF-SOFA scores of ACLF patients with bacterial infection were all high[31].

ACLF and ascites

Ascites at admission were a potential risk for post-enrollment development of ACLF in the study by Moreau *et al*, as it is an independent prognostic factor of renal failure following bacterial infection[15,32,33]. CLIF-SOFA scores at enrollment and ACLF diagnosis were significant independent predictors for post-enrollment ACLF development and ACLF-associated death, respectively[15].

ACLF and albumin-bilirubin

The albumin-bilirubin (ALBI) score, which uses albumin and bilirubin values to indicate liver injury, effectively predicts the outcome of hepatocellular carcinoma[34]. The ALBI score and the CLIF-SOFA score had a comparable effect in predicting the outcome of ACLF patients, according to the findings of Liu *et al*[35].

ACLF and hepatitis B virus

Hepatitis B virus (HBV) is the most common etiology of ACLF in the East, which differed from patients in Western societies. HBV-ACLF is a pan-Asian and African condition associated with excessively elevated short-term mortality[36]. In 2021, Li *et al*[37] created a new simple prognostic score that can accurately predict outcomes in HBV-ACLF patients. The C-indices of the new score were significantly higher than the C-indices of four existing scores (COSSH-ACLF, CLIF-C ACLF, MELD, and MELD-Na) for 28- and 90-d mortality. Without assessing organ failure, the novel prognostic score can correctly predict short-term mortality in patients with HBV-ACLF and could be used to guide clinical care[37]. In Taiwan, a viral hepatitis endemic country[38], a study demonstrated that APACHE III, CLIF-OF and CLIF-C ACLF scores have outperformed other models for predicting 28-d overall mortality[38].

ACLF and HRS

Terres *et al*[39] assessed and compared the significance of liver-specific scores in predicting mortality in hepatorenal syndrome (HRS) patients who received terlipressin. CTP was superior to CLIF-SOFA, CLIF-ACLF, MELD, and MELD-Na in estimating 30-d, 90-d, and 365-d mortality[39].

ACLF and AOVH

CTP was superior to CLIF-SOFA, CLIF-ACLF, MELD, and MELD-Na in estimating 30-d and 90-d mortality in AD patients, while CLIF-SOFA was better in ACLF patients with acute oesophageal variceal haemorrhage (AOVH) who received terlipressin[40].

ACLF and SBP

CLIF-SOFA has demonstrated superior performance in spontaneous bacterial peritonitis (SBP)[41] and alcoholic hepatitis[42].

ACLF and AKI

Both the standard and the modified CLIF-SOFA scores demonstrated remarkable accuracy for the prognostication of 28-d transplant free-mortality evaluation (AUC-ROC greater than 0.9) in acute kidney injury (AKI) patients with cirrhosis and AD. Nevertheless, it presents a reduced effectiveness in 90-d mortality assessment (AUC-ROC 0.78). These results are comparable to the results reported by Angeli *et al*[43] in 2015.

Hepatic and extra-hepatic injury

A study by Gupta *et al*[44] in 2017, that included hepatic and extra-hepatic ACLF patients showed that, in the hepatic group, iMELD was the best indicator of 28-d mortality. On the other hand, CLIF-SOFA was the strongest predictor of death in the extra-hepatic ACLF cohort. The majority of patients in this cohort were decompensated, and infection was the most frequent extra-hepatic event, leading to systemic inflammation and extra-hepatic organ involvement with fewer liver failures[44].

Critically unwell conditions

In predicting 90-d mortality, the SOFA score surpassed the more commonly used prognostic liver-specific scores (MELD, SOFA, CLIF-SOFA, CLIF-C OF, and CLIF-C ACLF/CLIF-C AD) in a study conducted to describe the best mortality risk factor(s) in critically unwell ACLF patients[45]. The CLIF-C ACLF, CLIF-C OF and ACLF grades varied widely between ACLF patients who underwent liver transplantation and those who died waiting for an organ. At the time of admission, those with two or three organ failures had survival rates ranging from 30% to 55%, whereas patients with more than three

organ failures had mortality rates approaching 80%[46].

AD and SARS-CoV-2

Mendizabal *et al*[47] performed a study to evaluate whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection affects the outcome of hospitalized cirrhotic patients and to assess the effectiveness of the different prognostic models in predicting mortality. CLIF-C scores performed better than North American Consortium for the Study of End-Stage Liver Disease (NACSELD)–ACLF score, CTP, and MELD-Na.

ACLF and alcohol intake

Aggressive alcohol intake, alcoholic hepatitis, and bacterial infection were the most common causes of ACLF in alcohol liver disease[48]. The AUROCs of the CLIF-SOFA, CLIF-OF, and CLIF-C scores showed a slight superior effect in estimating short-term mortality; however, they were equivalent to MELD and MELD-Na[49]. To clarify this finding, Chirapongsathorn *et al*[49] had elevated short- and long-term mortality rates. In patients with ACLF, as per the CLIF-C definition, the prediction accuracy of the CLIF-SOFA, CLIF-OF and CLIF-C scoring tools were no better than the accuracy of MELD and MELD-Na scores. In a retrospective investigation by Lee *et al*[50] the CLIF-SOFA score surpassed other scoring systems in estimating short-term mortality in alcoholic cirrhotic patients with AD.

Prognostic scores and liver transplantation

The MELD score is commonly used in liver transplantation (LT) as a scoring method for organ allocation and is the standard model prognostic tool for predicting 3-mo to 6-mo survival in patients with liver failure[51]. Nevertheless, ACLF has a distinct clinical characteristic (Table 5); therefore, the MELD score for patients with ACLF is not expected to be optimal[52].

The MELD score was associated with post-transplant survival but is considered to have poor prediction accuracy[53]. No more trials demonstrated that CLIF-SOFA, CLIF-C ACLF, or CLIF-C OF had good prognostic value for short-term survival after LT[52].

General comparison of prognostic scores

Despite the excellent predictive accuracy of CLIF-C ACLF and CLIF-C OF scores, they were developed analyzing data from patients generally with alcohol-related liver disease from Europe and the United States, and more research is necessary to confirm whether this is appropriate for Asian populations. However, according to the study by Zhang *et al*[14], the scores were also applicable in Asian populations.

A higher CLIF-SOFA was separately associated with higher mortality; this is consistent with previous research, which found that the CLIF-SOFA was better than other liver-specific scores in predicting mortality[42,54,55]. It has been shown by other researchers that CLIF-C ACLF or CLIF-C AD, MELD, and MELD-Na are preferred, even for extra-hepatic injuries[56,57].

In the study by Zhang *et al*[14], the prognostication accuracy and power of the six scores (CTP score, MELD score, MELD-Na, CLIF-ACLF score, CLIF-C OF score and CLIF-SOFA score) were analyzed and compared for 28-, 90- and 180-d overall mortality. The AUROC of CLIF-SOFA was superior to other predictive scores at 28-, 90-, and 180-d mortality, particularly at 28 d. The CLIF-SOFA score provides an overall and efficient evaluation of the severity of multi-organ failure in patients with ACLF by considering various systems, including the hepatic, respiratory, coagulation, circulatory, nervous, and renal systems. Zhang *et al*[14] and other researchers found that at all times, the CLIF-SOFA scores AUROCs were higher than those of other scores. A study performed by Perdigoto *et al*[58] showed that when ACLF is present, the CLIF-C OF score has good accuracy and is able to diagnose ACLF. MELD, on the other hand, performed better in terms of 90-d mortality prediction.

The CLIF-C ACLF score is the most accurate way to predict 28-d mortality in patients with ACLF. The CLIF-C AD score was also beneficial in predicting death in cirrhotic individuals with AD who did not meet diagnostic criteria for ACLF, although it did not outperform other well-established prognostication measures[59].

The CANONIC study found that 28-d mortality was 33.9%, while two Brazilian studies found that mortality rates in ACLF patients were 39%[56,60].

Within the included articles in this study from 2013 to 2022 (Figure 2), CLIF-SOFA was superior to other scores for predicting mortality (mostly in the short-term) in ACLF patients in more than 50% of the included articles, followed by CLIF-C ACLF and CLIF-C AD (30% of the articles)[61-89]. CLIF-C OF was more accurate at 10%. CTP accurately prognosticated ACLF patients with HRS and AOVH patients with AD. The MELD score accurately predicted short-term mortality in ACLF patients who underwent LT (Figure 3).

Table 5 Acute-on-chronic liver failure *vs* acute decompensation liver transplantation[45]

	Liver transplantation ACLF	Liver transplantation AD	*P* value
Total	22 (73.3%)	7 (26.7%)	-
Age (yr)	57.0 (IQR 11.0)	54.0 (IQR 5.0)	n.s.
MELD	30.7 (IQR 5.0)	12.9 (IQR 7.3)	< 0.001
iMELD	53.1 (IQR 8.7)	36.5 (IQR 15.6)	< 0.001
MELD-Na	34.4 (IQR 18.7)	14.3 (IQR 17.6)	0.002
CPC	13.0 (IQR 1.0)	9.0 (IQR 3.0)	< 0.001
SOFA	8.0 (IQR 3.0)	4.0 (IQR 3.0)	< 0.001
CLIF-SOFA	12.0 (IQR 3.0)	5.0 (IQR 3.0)	< 0.001
CLIF-C OF	11.5 (IQR 2.0)	7.0 (IQR 1.0)	< 0.001

ACLF: Acute-on-chronic liver failure; AD: Acute decompensation; MELD: Model of End-Stage Liver Disease; iMELD: integrated MELD; MELD-Na: sodium MELD; CPC: Child-Pugh class; SOFA: Sequential Organ Failure Assessment; CLIF-SOFA: CLIF-Consortium modification of Sequential Organ Failure Assessment; CLIF-C OF: Organ Failure score.

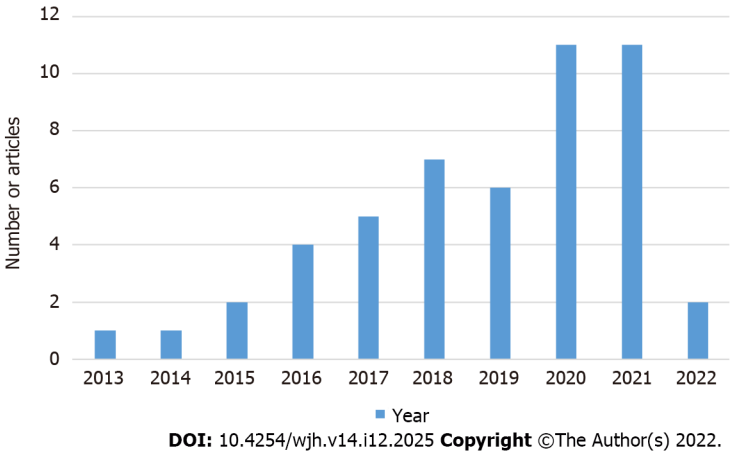

Figure 2 Year of publication.

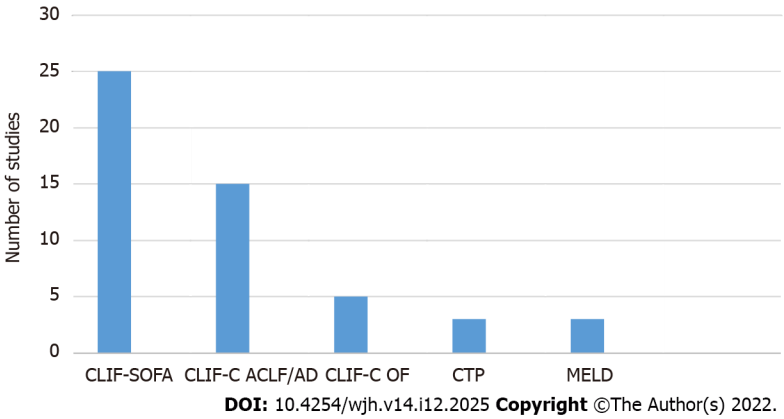

Figure 3 Predicting scores accuracy according to studies. ACLF: Acute-on-chronic liver failure; AD: Acute decompensation; CTP: Child-Turcotte-Pugh; SOFA: Sequential Organ Failure Assessment; CLIF-SOFA: CLIF-Consortium modification of Sequential Organ Failure Assessment; CLIF-C OF: Organ Failure score; MELD: Model of End-Stage Liver Disease.

CONCLUSION

The CLIF-SOFA score surpasses other predictive models in prognosticating short-term mortality in ACLF patients. CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD are accurate in predicting scores for short-term and long-term mortality in patients with ACLF and in predicting adverse outcomes associated with chronic liver disease.

ARTICLE HIGHLIGHTS

Research background

Acute-on-chronic liver failure is a syndrome characterized by decompensation in individuals with chronic liver disease, and is generally secondary to one or more extra-hepatic organ failures, implying an elevated mortality rate. Acute decompensation is the term used for one or more significant consequences of liver disease in a short time and is the most common reason for hospital admission in cirrhotic patients.

Research motivation

The European Association for the Study of Liver-Chronic-Liver Failure (EASL-CLIF) Group modified the intensive care Sequential Organ Failure Assessment score into CLIF-SOFA, which detects the presence of acute-on-chronic liver failure (ACLF) in patients with or without acute decompensation (AD), classifying it into three grades.

Research objectives

To investigate the role of the EASL-CLIF definition for ACLF and the ability of CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD scores for prognosticating ACLF or AD.

Research methods

This study is a literature review using a standardized search method, conducted using the steps following the guidelines for reporting systematic reviews set out by the PRISMA statement. Using specific keywords, relevant articles were found by searching PubMed, ScienceDirect, and BioMed Central-BMC. The databases were searched using the search terms by one reviewer (MSc student), and a list of potentially eligible studies was generated based on the titles and abstracts screened.

Research results

Most of the included studies used the EASL-CLIF definition for ACLF to identify cirrhotic patients with a significant risk of short-term mortality. The primary outcome in all reviewed studies was mortality. Most of the studies' findings were based on an AUROC analysis, which revealed that the CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD scores were preferable to other models in predicting 28-d mortality. They had the greatest AUROC scores predicting overall mortality at 90, 180, and 365 d. A total of 50 articles were included in this study, which found that the CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD scores could predict short-term and long-term mortality in patients with ACLF or AD in more than 50% of the articles found.

Research conclusions

The CLIF-SOFA score surpassed other predictive models in predicting short-term prognosis in ACLF patients. CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD are accurate in predicting scores for short-term and long-term mortality in patients with ACLF and in predicting adverse outcomes associated with chronic liver disease.

Research perspectives

Within the included articles in this study from 2013 to 2022, CLIF-SOFA was superior to other scores for predicting mortality (mainly in the short-term) in ACLF patients in more than 50% of the included articles, followed by CLIF-C ACLF and CLIF-C AD (30% of the articles). CLIF-C OF was accurate at 10%. CTP accurately predicted the score for ACLF patients with HRS and AOVH patients with AD. The MELD score accurately predicted short-term mortality in ACLF patients who underwent LT.

FOOTNOTES

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