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Original research

Performance of the China-CLIF framework in acute-on-chronic liver failure: a multicohort study across all aetiologies

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ABSTRACT

Background Acute-on-chronic liver failure (ACLF) of various aetiologies is a complex syndrome with high short-term mortality and significant global burden.

Objective To explore easily applicable diagnostic criteria and an accurate prognostic score for ACLF.

Design Clinical data from 5288 patients (after exclusions from 7388 screened) with acute deterioration of chronic liver disease across various aetiologies were used to evaluate the performance of European Chronic Liver Failure (CLIF) and Chinese Group on the Study of Severe Hepatitis B (COSSH) criteria. Three non-Asian cohorts were performed to validate the results.

Results CLIF criteria categorised 844 patients as ACLF (28-day/90-day liver transplantation (LT)-free mortality: 40.7%/57.0%; 321 with non-hepatitis B virus (HBV) aetiology, 523 with HBV aetiology), while COSSH criteria categorised 2038 patients as ACLF (mortality: 27.3%/41.0%; 602 with non-HBV aetiology, 1436 with HBV aetiology). COSSH criteria identified 22.6% (1194/5288) more patients (mortality: 19.1%/31.4%) compared with CLIF criteria, including 14.2% non-HBV patients (mortality: 15.9%/33.3%). COSSH criteria produced a more reasonable epidemiological pyramid-like distribution across severity grades (grades 1–3: 63.4%/27.5%/9.1% vs CLIF's grades 1–3: 25.8%/56.3%/17.9%). COSSH-ACLF II score showed the highest predictive values for 28-day/90-day LT-free mortality in both cirrhotic and all ACLF patients with various aetiologies, outperforming the CLIF-C ACLF and other scores. The comparable performance of China-CLIFs (renamed from COSSH-ACLFs) was validated in three non-Asian cohorts.

Conclusions This study evaluated the broader applicability of the China-CLIF framework across diverse aetiologies and varying severity levels of ACLF. These findings may provide a valuable foundation for harmonising ACLF diagnostic and prognostic system.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Acute-on-chronic liver failure (ACLF) can develop from various aetiologies and is a complicated clinical syndrome characterised by multiple organ failure and high short-term mortality.

⇒ Currently, no global prospective cohort study has established a unified diagnostic framework or simple, accurate prognostic scoring system for ACLF that is applicable across all disease aetiologies worldwide.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a complex syndrome that develops in patients with chronic liver disease of various aetiologies characterised by the acute deterioration of liver function and high short-term mortality.[1–4] To date, few global cohorts encompassing all aetiologies have been established to develop unified diagnostic criteria for ACLF.[5–8] Various definitions of ACLF have been proposed by different international consortia based on regional cohorts with specific aetiologies.[2 9 10] The main controversies involve the type of precipitating events (intrahepatic or extrahepatic), the stage of underlying chronic liver disease (chronic hepatitis or cirrhosis) and whether the definition should include extrahepatic organ failures.[9] The European criteria, proposed by the European Association for

WHAT THIS STUDY ADDS

⇒ This large prospective multicentre study evaluated the diagnostic performance of Chronic Liver Failure (CLIF) and Chinese Group on the Study of Severe Hepatitis B (COSSH) criteria and assessed the predictive ability of seven prognostic scores in ACLF patients across all aetiologies (hepatitis B virus (HBV) and non-HBV), with validation in three major non-Asian cohorts from Europe and Latin America.

⇒ Compared with the CLIF criteria, the COSSH criteria identified 22.6% more critically ill patients (including 14.2% with non-HBV aetiology) exhibiting organ failure and high short-term mortality that were not classified under CLIF criteria, while producing a more reasonable epidemiological pyramid-like distribution across severity grades conducive to early intervention.

⇒ The COSSH-ACLF II score demonstrated superior predictive accuracy for 28-day/90-day liver transplantation-free mortality across all aetiological subgroups, outperforming existing scoring systems, while the China-CLIF score showed comparable prognostic validity to the CLIF-C ACLF score in three independent non-Asian cohorts, confirming its global generalisability.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This prospective multicentre study, the first to include nearly all predominant ACLF aetiologies and to collaborate with major international cohorts, demonstrated that the China-CLIF framework showed a broader applicability across diverse aetiologies and geographic regions compared with existing systems. Our findings provide a valuable foundation for harmonising ACLF definitions, a critical step towards reducing global disparities in ACLF management and advancing therapeutic research.

the Study of Liver-Chronic Liver Failure (EASL-CLIF) Consortium, were first based on the multicentre prospective CANONIC (chronic liver failure consortium Acute-on-Chronic Liver Failure in Cirrhosis) cohort, which primarily included patients with alcohol-related and hepatitis C virus (HCV)-related liver disease. The Chinese Group on the Study of Severe Hepatitis B (COSSH) criteria were developed among patients with hepatitis B virus (HBV)-related chronic liver disease (with or without cirrhosis).[3] Both criteria include intrahepatic and extrahepatic precipitating events and emphasise the importance of both liver failure and extrahepatic organ failure,[11] despite some differences in clinical phenotypes—such as the frequency of organ failures—presumably attributable to aetiological differences. The 28-day and 90-day liver transplantation (LT)-free mortality rates of ACLF patients in the EASL-CLIF cohort were 34% and 51%, respectively (grade 1: 22%/41%; grade 2: 32%/52%; grade 3: 77%/79%), while similar mortality rates were observed in the COSSH-ACLF cohort at 33% and 52% (grade 1: 23%/36%; grade 2: 61%/74%; grade 3: 93%/100%).[3 4] These similarities demonstrate that both criteria effectively identify critically ill patients with comparable short-term mortality. The Asian Pacific Association for the Study of the Liver (APASL)-ACLF criteria can effectively recognise patients at an early stage of the disease.[12] The North American Consortium for the Study of End-Stage Liver Disease (NACSELD)-ACLF criteria include patients at a preterminal stage with two or more extrahepatic organ failures, predisposing these patients to extremely high mortality.[13]

This heterogeneity reflects not only differences in epidemiology but also varying conceptual understandings of ACLF—as a distinct syndrome, a complication of acute decompensation or the end-stage of liver disease. The existence of multiple definitions has led to significant confusion regarding the diagnosis and application of management recommendations for patients with ACLF.[8 9] Recently, there has been a significant change in the global burden of liver disease, with a decreasing prevalence of HCV/HBV and an increasing prevalence of risk factors such as alcohol addiction and drug abuse.[14 15] It remains urgent to explore whether these existing diagnostic frameworks can reliably and practically diagnose ACLF across the spectrum of current aetiologies. To address this, our large prospective multicentre study enrolled patients with diverse aetiologies and included validation from three non-Asian cohorts.

METHOD

Study design

Hospitalised patients with acute deterioration of chronic liver disease were prospectively screened and enrolled from a multicentre, open cohort. The study was conducted in three phases. First, we evaluated the clinical characteristics of patients using both CLIF and COSSH criteria (including epidemiology, organ failure, severity grade distribution and mortality). Second, we assessed the predictive performance of seven commonly used prognostic scores—COSSH-ACLF II score (COSSH-ACLF IIs), COSSH-ACLFs (modified from CLIF-C ACLFs, renamed to China-CLIFs), CLIF-C ACLFs, the Model for End-Stage Liver Disease (MELD), MELD-Na, MELD 3.0 and NACSELD-ACLF score (NACSELD-ACLFs)—for predicting 28-day/90-day LT-free mortality in ACLF patients with both non-HBV and HBV aetiologies, to explore whether a new score was needed. Third, the findings were validated in three non-Asian cohorts, covering ACLF patients from Europe and Latin America. Detailed clinical and follow-up data were collected via electronic data capture system and case report forms.

Patients

Patients hospitalised for more than 1 day with acute deterioration of chronic liver disease from all aetiologies were initially screened and enrolled from January 2018 to August 2023. Acute deterioration of chronic liver disease was divided into two subgroups: (1) severe liver injury (total bilirubin (TB) ≥5 mg/dL) based on diagnosed chronic liver disease and (2) acutely decompensated cirrhosis (ADC), characterised by ascites, hepatic encephalopathy (HE), upper gastrointestinal haemorrhage, bacterial infection or a high level of jaundice (TB≥5 mg/dL). The exclusion criteria, including the exclusion of patients with hepatocellular carcinoma, are summarised in figure 1. The diagnosis of cirrhosis was either biopsy-proven or based on the usual clinical, laboratory, endoscopic and radiologic diagnostic criteria. The duration of underlying non-cirrhotic chronic liver disease should be longer than 6 months. We conducted a power analysis to achieve our main aim (the first phrase) based on the following assumptions: the estimated 28-day LT-free mortality rate of the non-ACLF group is 3%,[3] the relative risk in the ACLF group is at least 2,[4] the estimated sample size ratio between the non-ACLF and ACLF groups is 1:3. Considering a 5% two-sided type I error (α) and 5% dropout rate, at least 4011 patients were needed to achieve a power of 95%. Clinical data, including demographic data, cirrhosis complications and

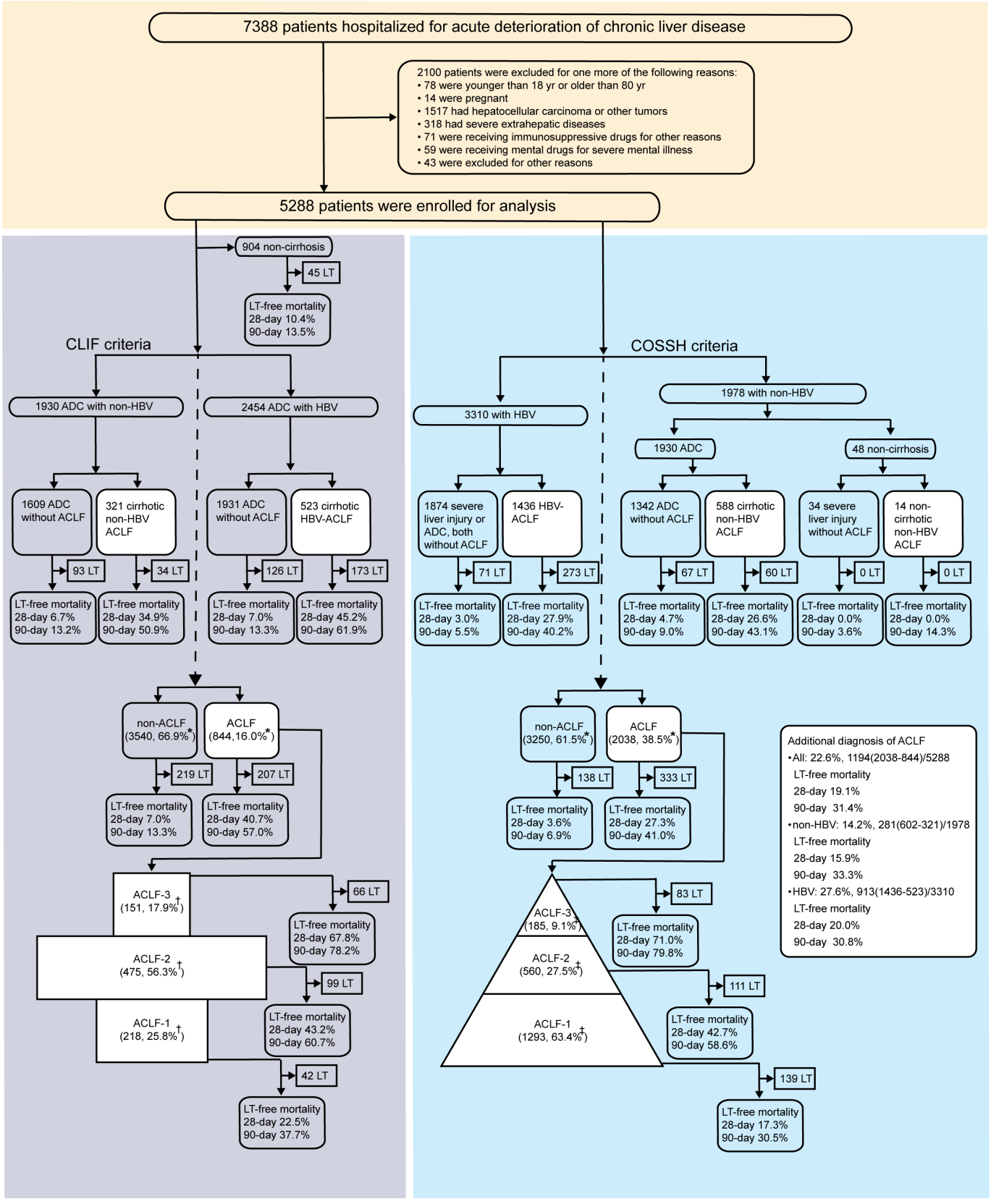

Figure 1 Patients were screened, enrolled and classified according to the CLIF or COSSH criteria. *The percentage of individuals out of 5288 patients; †The percentage of individuals out of 844 patients; ‡The percentage of individuals out of 2038 patients. ACLF, acute-on-chronic liver failure; ADC, acutely decompensated cirrhosis; CLIF, Chronic Liver Failure; COSSH, Chinese Group on the Study of Severe Hepatitis B; HBV, hepatitis B virus; HBV-ACLF, HBV-related ACLF; LT, liver transplantation.

laboratory indicators, were collected at admission. Patients were followed up for at least 90 days after enrolment. Information regarding LT and survival time and status at days 28 and 90 after enrolment was also collected.

During hospitalisation, patients were managed in an intensive care unit and received integrative treatment strategies under clinical guidelines. These included rapid restoration of metabolic and haemodynamic stability; nutritional support and specific treatments for conditions such as ascites, infections, HE and gastrointestinal haemorrhage. Patients were administered human serum albumin infusion or plasma transfusion when necessary. All HBV-related patients received antiviral therapy according to the established consensus. For patients with severe liver dysfunction, extracorporeal liver support modalities—including plasma exchange, haemofiltration, haemoperfusion and plasma molecular adsorption systems—were used. Renal replacement therapy (RRT) was initiated in cases of hepatorenal syndrome-acute kidney injury refractory to pharmacological therapy, particularly when accompanied by volume overload, severe electrolyte derangements or uraemia. The primary RRT modalities employed were continuous RRT, intermittent RRT and intermittent haemodialysis. Haemodynamic support with vasopressors was administered for persistent hypotension (mean arterial pressure <65 mm Hg) despite adequate fluid resuscitation. Mechanical ventilation was instituted primarily for airway protection in patients with grade III/IV HE or for severe hypoxaemia (defined as a PaO_2/FiO_2 ratio <200 mm Hg). The number of ACLF patients receiving extracorporeal support during hospitalisation is provided in online supplemental table 1. Patients in the current study were recommended to be listed for LT according to the EASL Clinical Practice Guidelines for LT.[16] The degree of medical urgency was determined by the MELD score, with a higher score indicating a higher priority. All donor livers in this study were acquired from donation after brain death or cardiac death, which were all strictly in accordance with the Chinese guidelines on liver donation and the Declaration of Helsinki.

Diagnostic criteria and scoring systems

ACLF was evaluated at admission. The detailed information on CLIF, COSSH and APASL criteria and organ failure definition is provided in online supplemental table 2. The formulas of seven prognostic scores (COSSH-ACLF IIs/China-CLIFs/CLIF-C ACLFs/MELD/MELD-Na/MELD 3.0/NACSELD-ACLFs) are provided in the online supplemental methods.

Three non-Asian validation cohorts

Patients hospitalised for ADC (defined as ascites, HE, gastrointestinal haemorrhage, infection or any combination of these) were non-selectively enrolled from three non-Asian multicentre, prospective validation cohorts from Europe and Latin America: CANONIC, PREDICT (PREDICTing Acute-on-Chronic Liver Failure) and ACLARA (Prevalence, Epidemiology, Characterization, and Mechanisms of Acute-on-Chronic Liver Failure in Latin America).[4 17–19] The predictive ability of prognostic scores for 28-day/90-day LT-free mortality was assessed in ACLF patients, according to CLIF criteria.

Since urea, the key predictor of COSSH-ACLF IIs, was not collected in the three non-Asian cohorts, external validation of the COSSH-ACLF IIs could not be performed in these populations. Considering the difference in the organ failure between COSSH and CANONIC cohorts, a matching analysis was conducted based on the organ failure distribution observed in the CANONIC cohort (liver, renal, cerebral, coagulation, circulatory, respiratory failure: 43.6%, 55.8%, 24.1%, 27.7%, 16.8%, 9.2%).[4] This analysis included patients with non-HBV aetiologies who met CLIF criteria within the derivation cohort. Patients with the least frequent organ failures were prioritised to determine the maximum number of patients that could be matched. If the number of eligible patients exceeded the required sample size, the final selection was performed through random sampling.

Statistical analysis

Continuous variables are reported as mean±SD for normally distributed data or median (first quartile (Q1), third quartile (Q3)) for non-normally distributed data. Categorical variables are expressed as percentages (numbers), unless the cell count is less than 20, in which case data are reported as numbers only. Normality was assessed using histograms, Q-Q plots and the Kolmogorov-Smirnov test. Homogeneity of variance was assessed by Levene's test. For continuous variables, the Student's t-test and one-way analysis of variance were used for two-group and multigroup comparisons with normally distributed data and homogeneity of variance, while Welch's t-test was applied when homogeneity was violated; if normality or homogeneity was not met, the Mann-Whitney U test and Kruskal-Wallis test were used for two-group and multigroup comparisons, respectively. For a 2-by-2 table, Fisher's exact test is used to analyse categorical data if any expected cell count is less than 5, otherwise the χ^2 test is used. The area under the receiver operating characteristic curve (AUROC) was calculated, and the Z test (Delong's method) compared the predictive value of scoring systems. A U-statistics-based C estimator that is asymptotically normal was calculated, and the z-score test was used to compare two concordance indexes (C-indexes). Calibration was assessed by calibration curves and goodness-of-fit with the Hosmer-Lemeshow statistic test; and overall performance was tested using the R^2 and Brier scales. Better performance is indicated by a higher R^2 and a lower Brier scale score. Survival analysis used Kaplan-Meier with log-rank test for comparing the cumulative incidence of death across 3 risk strata. HRs with 95% CIs were calculated using Cox regression (the low-risk stratum as reference), with confirmation of proportional hazards via Schoenfeld residuals ($p>0.05$). The start time coincides with the origin time, and the end time will be defined as the time of death, loss to follow-up or the end of 28/90 days study period. A two-tailed $p<0.05$ was considered statistically significant. Statistical analysis details are provided in the Statistical Analysis Plan of online supplemental materials. We did a sensitivity analysis by excluding 103 HBV-related ACLF patients, included in the initial derivation cohort of the COSSH-ACLF IIs, to ascertain whether including overlapping samples affected the results. R V.4.0.2 (https://www.r-project.org) and SPSS software V.25 (SPSS) were used to perform the statistical analyses.

RESULTS

Patients in the all-aetiology cohort

Out of 7388 initially screened patients, 5288 with acute deterioration of chronic liver disease from various aetiologies were enrolled in this prospective multicentre study (figure 1). Among them, 62.6% (3310) had HBV-related aetiology, and 37.4% (1978) had non-HBV aetiologies. The non-HBV aetiology included alcohol (42.2%), autoimmune (21.3%), parasite- (5.0%), drug- (2.6%) and HCV (2.4%) related chronic liver diseases (online supplemental table 3). According to CLIF criteria, 844 (16.0%) patients were categorised as ACLF, including 321 with non-HBV and 523 with HBV aetiologies. HBV-related ACLF patients demonstrated higher proportions of liver (88.3% vs 75.7%) and coagulation failures

(67.5% vs 44.2%), while non-HBV patients showed significantly greater renal failure prevalence (38.9% vs 16.8%). According to COSSH criteria, 2038 (38.5%) patients were categorised as ACLF, including 602 with non-HBV aetiology and 1436 with HBV aetiology. HBV-related ACLF patients exhibiting higher liver failure proportions (94.9% vs 86.7%) and non-HBV patients maintaining renal failure predominance (20.9% vs 6.6%). Detailed organ failure distributions under both diagnostic criteria are exhibited in table 1 and online supplemental table 4. The median follow-up time of ACLF patients was 90 days. At 90 days, 3.3% (67/2038) of ACLF patients were lost to follow-up. The primary reason for loss to follow-up was inability to contact the patients.

Performance of CLIF and COSSH criteria for diagnosis

The key difference between CLIF and COSSH criteria is that COSSH criteria included patients without cirrhosis and an additional subgroup of patients with single liver failure plus 1.5<international normalised ratio (INR)≤2.5. Compared with CLIF criteria, COSSH criteria identified an additional 22.6% (1194) of patients as ACLF, including an additional 14.2% (281) in patients with non-HBV aetiology and an additional 27.6% (913) in patients with HBV aetiology (figures 1 and 2A). Among these additionally identified patients, 67.9% (811) had cirrhosis and 32.1% (383) had no cirrhosis (online supplemental table 5). A grade-by-grade comparison of patients from non-ACLF to ACLF under CLIF and COSSH criteria is provided in figure 3. The 28-day/90-day LT-free mortality rates of these additional patients were 19.1%/31.4%, exceeding the 15% mortality threshold raised from CLIF criteria[4] (cirrhosis/non-cirrhosis: 17.6%/22.3%, 32.6%/28.8%; ACLF-1/2/3: 16.3%/29.3%, 40.0%/47.1%, 88.2%/88.2%; see online supplemental tables 5 and 6). Notably, the 28-day LT-free mortality of the additional subgroup of patients with single liver failure plus 1.5≤INR<2.5 with non-HBV aetiology also exceeded the 15% threshold (online supplemental table 7). These findings suggest that such patients qualify as ACLF-1. The comparative analysis of the APASL criteria with the CLIF and COSSH criteria is presented in figure 2B. It should be noted that the history of prior decompensation was not collected in a subset of patients in this study. Compared with the APASL criteria, the CLIF and COSSH criteria identified an additional 6.5% and 18.4% of patients as ACLF. However, 4.5% of patients identified exclusively by the APASL criteria exhibited relatively milder clinical features, with a 28-day LT-free mortality rate of 9.5%, which did not meet the 15% threshold. The clinical characteristics of such patients are detailed in online supplemental table 8.

The analysis of grade distribution (table 2) revealed that approximately 25.8%, 56.3% and 17.9% of the 844 ACLF patients under CLIF criteria were classified as ACLF-1, ACLF-2 and ACLF-3, respectively. The number of ACLF-2 patients was significantly higher than ACLF-1 and ACLF-3 in both non-HBV and HBV aetiology groups. Approximately 63.4%, 27.5% and 9.1% of the 2038 ACLF patients under COSSH criteria were classified as ACLF-1, ACLF-2 and ACLF-3, respectively. The reasonable epidemiological pyramid-like distribution across severity grades was consistent in different aetiologies. The follow-up analysis (table 2) showed that the 28-day/90-day LT-free mortality rates of all ACLF patients who met COSSH criteria were comparatively lower than those who met CLIF criteria (27.3%/41.0% vs 40.7%/57.0%, all p<0.0001; non-HBV-related: 25.9%/42.7% vs 34.9%/50.9%, p=0.0060/=0.028; HBV-related: 27.9%/40.2% vs 45.2%/61.9%, both p<0.0001).

Clinical characteristics of ACLF under COSSH criteria

The clinical characteristics of patients with all aetiologies under COSSH criteria are summarised in online supplemental table 4. Compared with the non-ACLF patients, the ACLF patients were younger (50.8±12.2 vs 53.9±12.5, p<0.0001). Laboratory indicators, including TB, INR, serum creatinine, C reactive protein and white cell count and organ failure frequency, were significantly worse in ACLF patients than in non-ACLF patients (all p<0.0001). All scores (COSSH-ACLF IIs/China-CLIFs/CLIF-C ACLFs/MELD/MELD-Na/MELD 3.0) were significantly greater in ACLF patients than in non-ACLF patients (all p<0.0001). LT-free mortality rates (28/90 days) were significantly higher in ACLF patients compared with non-ACLF patients (27.3%/41.0% vs 3.6%/6.9%, p<0.0001).

Liver failure was the most frequent type of organ failure in both ACLF patients with non-HBV and HBV aetiology, demonstrating the core definition of 'liver failure' in this complicated syndrome (table 1). Compared with ACLF patients with an HBV aetiology, ACLF patients with a non-HBV aetiology were older (53.9±12.3 vs 49.4±11.9, p<0.0001) and had a higher prevalence of cirrhosis and complications. Alcohol-related ACLF patients exhibited the highest level of inflammatory response (higher C reactive protein levels, white blood cell counts and neutrophil counts) than those with autoimmune-related and other non-HBV aetiologies (online supplemental table 9). Follow-up analysis showed no significant difference in 28-day/90-day LT-free mortality between the two groups under COSSH criteria (p=0.39/0.32), but a significant difference under CLIF criteria (non-HBV, 34.9%/50.9%; HBV, 45.2%/61.9%, p=0.0068/0.0061) (table 1), further indicating the outperformance of COSSH criteria for ACLF diagnosis for all aetiologies.

Prognostic performance of COSSH-ACLF IIs in the derivation cohort

Under CLIF criteria, ROC curve and C-index analysis (figure 4A and online supplemental table 10) showed COSSH-ACLF IIs had the best discrimination for predicting 28-day/90-day LT-free mortality in all cirrhotic ACLF patients compared with other scores, with higher AUROC in ACLF patients with non-HBV aetiology (0.803 (0.751–0.855)/0.781 (0.727–0.836)), and similar results were observed in ACLF patients with HBV aetiology (online supplemental figure 1A). When considering LT and mortality as equivalent endpoints, ROC curve analysis also showed that COSSH-ACLF IIs had the better prognostic performance than CLIF-C ACLFs, MELD, MELD-Na, MELD 3.0 and NACSELD-ACLFs (online supplemental figure 2). Additionally, COSSH-ACLF IIs exhibited a better calibration performance (online supplemental figure 3). These results indicated that COSSH-ACLF IIs showed outperformance in cirrhosis patients.

Under COSSH criteria, ROC curve and C-index analysis (figure 4B, online supplemental figure 1B and table 10) also showed COSSH-ACLF IIs had the equivalent discrimination to China-CLIFs for predicting the 28-day/90-day LT-free mortality of all ACLF patients, significantly outperforming the five other scores. As the previous study described, 2 optimal cut-off values of COSSH-ACLF IIs (7.4/8.4) can be used to separate ACLF patients into three risk strata of death at 28 days (low/intermediate/high risk: <7.4/7.4–8.4/≥8.4).[20] In this study, the

Table 1 Clinical characteristics of patients with ACLF under CLIF criteria and COSSH criteria

Characteristic	CLIF criteria				COSSH criteria			
	All (n=844)	Non-HBV (n=321)	HBV (n=523)	P value*	All (n=2038)	Non-HBV (n=602)	HBV (n=1436)	P value†
Age (years)	52.3±12.0	54.7±12.7	50.8±11.4	<0.0001	50.8±12.2	53.9±12.3	49.4±11.9	<0.0001
Male (no.)	74.9% (632)	65.7% (211)	80.5% (421)	<0.0001	78.9% (1608)	63.3% (381)	85.4% (1227)	<0.0001
Cirrhosis (no.)	100.0% (844)	100.0% (321)	100.0% (523)	1.0	81.2% (1655)	97.7% (588)	74.3% (1067)	<0.0001
Complication								
HE	40.9% (345)	37.7% (121)	42.8% (224)	0.14	20.2% (412)	20.6% (124)	20.1% (288)	0.78
GIH	11.2% (93)	13.4% (43)	9.8% (50)	0.11	7.0% (142)	10.1% (61)	5.7% (81)	0.00037
Ascites	75.0% (633)	71.3% (229)	77.2% (404)	0.054	65.3% (1331)	69.6% (419)	63.5% (912)	0.0084
Infection	55.1% (465)	61.7% (198)	51.1% (267)	0.0026	44.3% (902)	55.3% (333)	39.6% (569)	<0.0001
Laboratory data								
ALT (U/L)	82.0(34.0, 237.0)	42.0(23.0, 88.8)	130.0(54.0, 377.5)	<0.0001	124.0(49.0, 370.8)	48.0(26.0, 108.5)	190.0(76.0, 504.0)	<0.0001
AST (U/L)	109.0(57.2, 223.3)	78.0(48.0, 144.3)	134.5(73.2, 284.8)	<0.0001	136.0(75.0, 273.3)	95.5(56.0, 175.0)	152.0(87.3, 322.3)	<0.0001
ALP (U/L)	127.5(95.0, 167.0)	126.0(89.0, 180.5)	129.0(97.0, 160.5)	0.77	137.2(107.0, 175.0)	139.0(107.0, 179.8)	137.0(108.0, 173.0)	0.38
GGT (U/L)	62.0(36.0, 110.8)	64.0(31.0, 143.0)	60.0(37.0, 95.0)	0.099	77.5(46.0, 124.0)	81.0(39.3, 169.8)	76.0(49.0, 116.0)	0.018
Alb (g/L)	29.7±5.0	28.5±5.1	30.5±4.9	<0.0001	30.2±4.8	28.3±4.8	31.0±4.6	<0.0001
TB (μmol/L)	338.1(240.1, 461.9)	294.5(206.9, 428.9)	355.7(266.6, 467.8)	<0.0001	334.5(254.7, 433.0)	300.1(235.6, 426.5)	341.5(266.3, 436.2)	<0.0001
Creatinine (μmol/L)	90.0(61.0, 177.0)	139.0(75.0, 223.0)	77.0(56.9, 139.0)	<0.0001	69.0(56.0, 95.0)	84.0(60.0, 145.0)	65.0(55.0, 82.0)	<0.0001
Serum urea (mmol/L)	7.7(4.4, 15.0)	11.4(6.8, 19.2)	6.0(3.7, 11.1)	<0.0001	5.0(3.5, 8.5)	7.2(4.3, 13.8)	4.5(3.2, 6.9)	<0.0001
Sodium (mmol/L)	136.3±6.4	135.1±7.2	137.1±5.8	<0.0001	136.7±5.3	135.2±6.4	137.3±4.7	<0.0001
CRP (mg/L)	13.1(7.7, 26.5)	18.2(9.1, 35.4)	11.3(7.2, 19.4)	<0.0001	12.6(7.7, 21.9)	18.0(9.9, 33.5)	11.4(7.3, 17.9)	<0.0001
WCC (10^9/L)	7.4(5.1, 11.4)	7.7(5.0, 12.9)	7.3(5.1, 10.3)	0.064	6.9(5.0, 9.9)	7.2(4.9, 11.9)	6.9(5.0, 9.5)	0.0024
Neutrophil (10^9/L)	5.5(3.5, 9.1)	5.6(3.5, 10.3)	5.4(3.5, 8.4)	0.036	5.0(3.3, 7.7)	5.3(3.4, 9.6)	4.9(3.3, 7.1)	<0.0001
Haemoglobin (g/L)	101.3±27.7	89.5±26.2	108.7±25.9	<0.0001	110.6±26.9	92.0(74.0, 110.0)	121.0(103.0, 134.3)	<0.0001
Haematocrit (%)	29.2±8.0	26.0±7.3	31.2±7.8	<0.0001	31.6±7.6	26.5(22.5, 31.3)	33.8(29.2, 38.3)	<0.0001
Platelet count (10^9/L)	69.0(43.0, 111.0)	74.0(46.0, 120.0)	67.0(41.0, 105.0)	0.083	86.0(53.0, 130.0)	81.0(50.0, 132.0)	89.0(54.5, 129.0)	0.25
INR	2.6(1.9, 3.1)	2.3(1.6, 2.8)	2.7(2.2, 3.2)	<0.0001	2.0(1.7, 2.6)	1.9(1.6, 2.4)	2.1(1.7, 2.6)	<0.0001
Severity score								
COSSH-ACLF IIs	8.1±1.1	8.1±1.1	8.1±1.0	0.75	7.5±1.1	7.7±1.1	7.4±1.0	<0.0001
China-CLIFs	7.2±1.6	7.0±1.2	7.4±1.8	<0.0001	6.6±1.4	6.5±1.1	6.6±1.5	0.030
CLIF-C ACLFs	48.2±8.1	48.2±8.5	48.3±7.9	0.90	43.9±8.2	45.0±8.2	43.4±8.1	<0.0001
MELD	27.2±7.9	25.8±8.3	28.1±7.4	<0.0001	23.7±7.0	22.3±7.7	24.3±6.6	<0.0001
MELD-Na	28.6±7.3	27.6±7.7	29.1±6.9	0.0026	25.2±6.6	24.4±7.3	25.5±6.3	0.0016
MELD 3.0	31.9±5.9	32.1±6.4	31.9±5.7	0.66	29.1±5.0	29.9±5.4	28.8±4.8	<0.0001
Organ failure								
Liver	83.5% (705)	75.7% (243)	88.3% (462)	<0.0001	92.5% (1885)	86.7% (522)	94.9% (1363)	<0.0001
Coagulation	58.6% (495)	44.2% (142)	67.5% (353)	<0.0001	29.8% (608)	23.9% (144)	32.3% (464)	0.00016
Cerebral	16.8% (142)	15.0% (48)	18.0% (94)	0.26	8.8% (180)	8.5% (51)	9.0% (129)	0.71
Renal	25.2% (213)	38.9% (125)	16.8% (88)	<0.0001	10.8% (221)	20.9% (126)	6.6% (95)	<0.0001
Respiratory	7.7% (65)	4.4% (14)	9.8% (51)	0.0044	3.7% (76)	2.3% (14)	4.3% (62)	0.030

Continued

Table 1 Continued

Characteristic	CLIF criteria				COSSH criteria			
	All (n=844)	Non-HBV (n=321)	HBV (n=523)	P value*	All (n=2038)	Non-HBV (n=602)	HBV (n=1436)	P value†
Circulation	7.1% (60)	9.3% (30)	5.7% (30)	0.048	3.3% (67)	5.0% (30)	2.6% (37)	0.0054
Transplant-free mortality								
28 days	40.7% (274)	34.9% (103)	45.2% (171)	0.0068	27.3% (483)	25.9% (145)	27.9% (338)	0.39
90 days	57.0% (352)	50.9% (141)	61.9% (211)	0.0061	41.0% (676)	42.7% (221)	40.2% (455)	0.32

Among 5288 patients with acute deterioration of chronic liver disease, 844 patients were categorised as ACLF under CLIF criteria, including 321 with non-HBV and 523 with HBV aetiologies. According to COSSH criteria, 2038 patients were categorised as ACLF under COSSH criteria, including 602 with a non-HBV aetiology and 1436 with an HBV aetiology. Categorical variables are expressed as percentages (n); continuous variables are expressed as either the mean±SD or median (Q1–Q3). (Student's t-test, Mann-Whitney U test, χ^2 test or Fisher's exact test).
*P values for comparisons between ACLF patients with and without HBV aetiology under CLIF criteria.
†P values for comparisons between ACLF patients with and without HBV aetiology under COSSH criteria.
ACLF, acute-on-chronic liver failure; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C, Chronic Liver Failure Consortium; COSSH, Chinese Group on the Study of Severe Hepatitis B; CRP, C reactive protein; GGT, glutamyl transferase; GIH, gastrointestinal haemorrhage; HE, hepatic encephalopathy; INR, international normalised ratio; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; TB, total bilirubin; WCC, white cell count.

28-day/90-day LT-free mortality of ACLF patients with all aetiologies under COSSH criteria significantly differed among the three groups (low risk: 11.3% (9.3%–13.3%)/20.9% (18.2%–23.5%), intermediate risk: 35.2% (31.0%–39.2%)/49.1% (44.4%–53.4%), high risk: 72.4% (61.0%–72.4%)/76.7% (70.9%–81.4%), p<0.0001) (online supplemental figure 4). Compared with the low-risk group, the HRs of death at 28/90 days in the intermediate-risk and high-risk groups reached 3.61 (2.85–4.58)/2.97 (2.45–3.60) (both p<0.0001) and 10.69 (8.40–13.60)/7.91 (6.46–9.68) (both p<0.0001). Similar results were observed in ACLF patients with HBV and non-HBV aetiology. Further survival analysis showed that the above three groups had significant differences in 28-day/90-day mortality regardless of whether LT was treated as a censoring event or as an endpoint equivalent to death (online supplemental figures 5 and 6). Excluding overlapping samples from the initial derivation cohort did not affect the results (online supplemental figure 7). Subgroup analysis showed that COSSH-ACLF IIs had a similar prognostic performance after removing ADC patients identified only with bacterial infection or jaundice (online supplemental figure 8). These results indicated that COSSH-ACLF IIs had the best prognostic performance for predicting the short-term mortality of ACLF patients with all aetiologies.

VALIDATION IN THE NON-ASIAN POPULATIONS

A total of 4072 patients with ADC from these non-Asian cohorts were analysed for validation, with 1030 patients categorised as ACLF based on CLIF criteria (table 3). ROC curve analysis of these 1030 ACLF patients (figure 4C) showed that China-CLIFs performed equivalently to CLIF-C ACLFs at both 28 and 90 days, and significantly outperformed MELD, MELD-Na, MELD 3.0 and NACSELD-ACLFs. These results indicated that China-CLIFs were also applicable for non-Asian cirrhotic populations.

Since urea (a key predictor in the COSSH-ACLF IIs) was not collected in the three non-Asian cohorts, external validation could not be performed. A mimic validation was conducted by a matching analysis of 321 non-HBV ACLF patients, of which 133 (with organ failure rates: liver 46.6%, renal 57.9%, cerebral 23.3%, coagulation 25.6%, circulatory 17.3%, respiratory 9.8%) were matched to ACLF patients of the CANONIC cohort (table 4). ROC curve analysis (figure 4D) showed that the COSSH-ACLF IIs demonstrated equivalent discriminatory ability to the China-CLIFs in predicting 28-day LT-free mortality and comparable performance to China-CLIFs, CLIF-C ACLFs, MELD 3.0 in predicting 90-day LT-free mortality. It outperformed five other scores for 28-day LT-free mortality and three other scores for 90-day LT-free mortality.

DISCUSSION

ACLF is widely recognised as a complex condition with high short-term mortality, underlining the necessity for an easily applicable diagnostic framework to enhance patient management. Both CLIF-ACLF and COSSH-ACLF definitions are evidence-based, originally developed based on different aetiological patient populations. This prospective multicentre study, encompassing 9360 patients (5288 with diverse aetiologies, plus validation from three non-Asian cohorts totalling 4072 patients), provides an effective analysis of the China-CLIF framework for ACLF, offering some potential evidence for addressing the urgent need.

Given the significant changes in the current global aetiologies of ACLF,[15 21–23] a large prospective multicentre cohort encompassing all aetiologies is essential for evaluating an easily

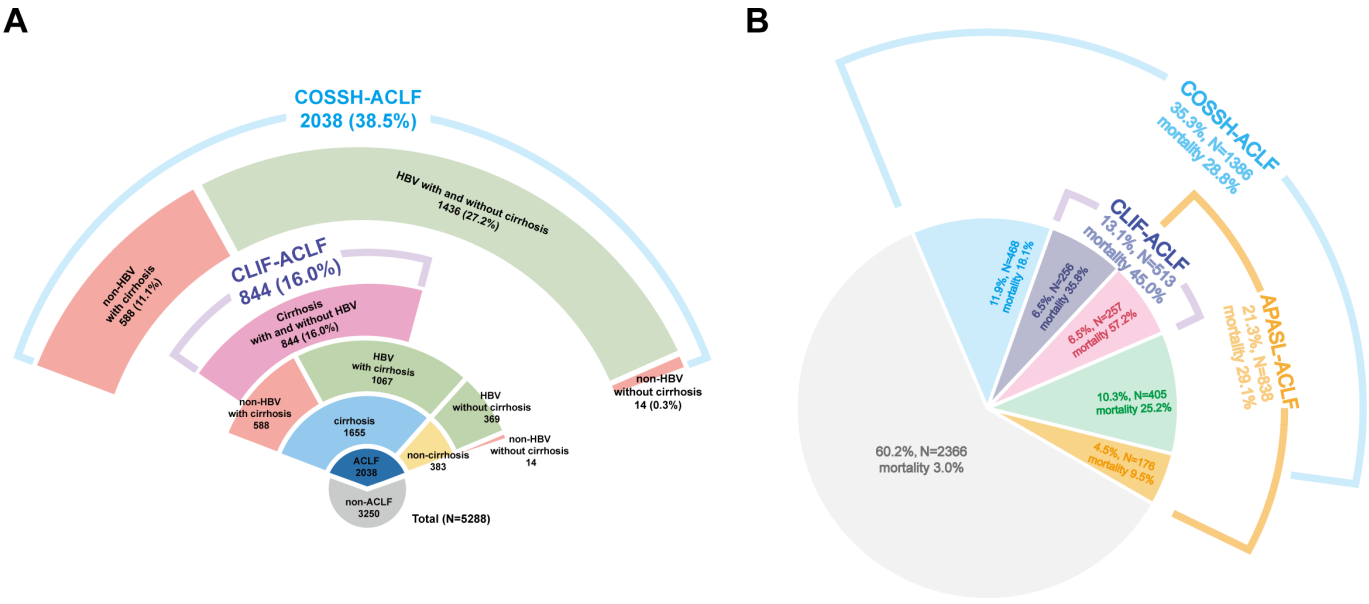

Figure 2 Fan-shaped diagram of diagnostic performance of the CLIF, COSSH and APASL criteria. (A) Diagnostic performance of the CLIF and COSSH criteria in 5288 patients; (B) The distribution of 3928 patients according to APASL, COSSH and CLIF criteria with 28-day LT-free mortality. ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the study of the liver; CLIF, Chronic Liver Failure; COSSH, Chinese Group on the Study of Severe Hepatitis B; LT, liver transplantation.

applicable diagnostic framework for ACLF. This new prospective multicentre study covered almost all the different aetiologies including currently predominant HBV-related and non-HBV-related ACLF. The analysis of clinical characteristics in ACLF patients showed comparatively lower rates of extrahepatic organ failure in the HBV-related population, whereas alcohol- and autoimmune-related patients exhibited higher rates, indicating differences in aetiologies. This phenotype of higher extrahepatic organ failure was particularly evident in the EASL-CLIF cohorts, as they primarily included patients with alcohol-related and HCV-related ACLF.[4] Notably, the global incidence of HCV-related ACLF has significantly decreased worldwide in recent years, which may affect the current distribution of ACLF aetiologies.[15] This study provides a chance to evaluate the broader applicability of the China-CLIF framework, especially in the absence of global prospective cohorts.

Comparative studies of different definitions to explore cross-regional applicability are highly encouraged, as they contribute to valuable advancements in clinical management.[24–26] Sensitivity and specificity are important for easily applicable diagnostic criteria for ACLF of all aetiologies. Both CLIF and COSSH criteria were designed to identify critically ill patients with high short-term mortality across severity grades, as highlighted in the original studies and subsequent reviews.[1–4 10] Recent studies demonstrated that CLIF criteria perform better than APASL and NACSELD criteria in alcohol-related and HCV-related ACLF patients,[24 26] and COSSH criteria have better sensitivity than CLIF criteria in HBV-related ACLF patients.[3 27] In this new all-aetiology cohort, the CLIF criteria identified 16.0% of patients as ACLF, while COSSH criteria captured these along with an additional 22.6% critically ill patients of the entire derivation cohort excluded by CLIF criteria. These additional patients

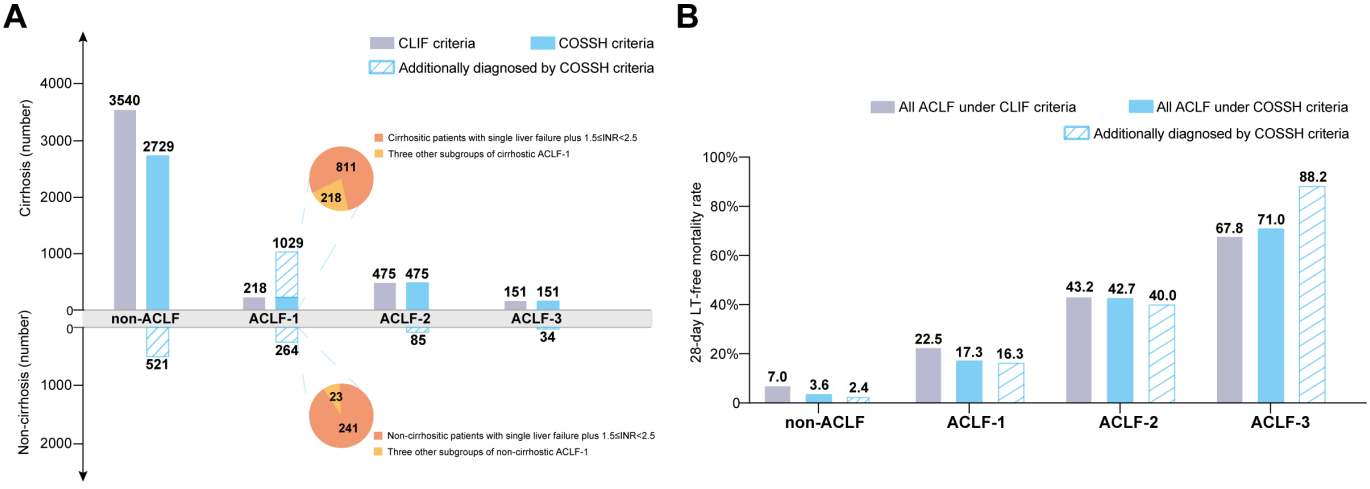

Figure 3 A grade-by-grade comparison under CLIF and COSSH criteria. (A) Patient distribution from non-ACLF to ACLF-3; (B) The 28-day LT-free mortality rate of non-ACLF to ACLF-3. ACLF, acute-on-chronic liver failure; CLIF, Chronic Liver Failure; COSSH, Chinese Group on the Study of Severe Hepatitis B; LT, liver transplantation.

Table 2 The prevalence and 28-day/90-day liver transplantation-free mortality of patients with ACLF under CLIF and COSSH criteria

	Prevalence			28-day LT-free mortality			90-day LT-free mortality		
Type of ACLF	CLIF	P value*	COSSH	CLIF	COSSH	P value†	CLIF	COSSH	P value†
ACLF	N=844		N=2038	40.7% (274/673)	27.3% (483/1770)	<0.0001	57.0% (352/618)	41.0% (676/1650)	<0.0001
ACLF-1	25.8% (218/844)	<0.0001	63.4% (1293/2038)	22.5% (42/187)	17.3% (206/1192)	0.087	37.7% (63/167)	30.5% (340/1114)	0.062
ACLF-2	56.3% (475/844)		27.5% (560/2038)	43.2% (171/396)	42.7% (201/471)	0.88	60.7% (221/364)	58.6% (253/432)	0.54
ACLF-3	17.9% (151/844)	<0.0001	9.1% (185/2038)	67.8% (61/90)	71.0% (76/107)	0.62	78.2% (68/87)	79.8% (83/104)	0.78
HBV-related	62.0% (523/844)		70.5% (1436/2038)	45.2% (171/378)	27.9% (338/1211)	<0.0001	61.9% (211/341)	40.2% (455/1133)	<0.0001
ACLF-1	20.1% (105/523)	<0.0001	62.9% (903/1436)	25.0% (21/84)	17.2% (143/829)	0.078	44.4% (32/72)	29.4% (229/779)	0.0081
ACLF-2	60.8% (318/523)		27.8% (399/1436)	47.4% (119/251)	46.3% (149/322)	0.79	64.2% (147/229)	60.3% (179/297)	0.36
ACLF-3	19.1% (100/523)	<0.0001	9.3% (134/1436)	72.1% (31/43)	76.7% (46/60)	0.60	80.0% (32/40)	82.5% (47/57)	0.76
Non-HBV-related	38.0% (321/844)		29.5% (602/2038)	34.9% (103/295)	25.9% (145/559)	0.0060	50.9% (141/277)	42.7% (221/517)	0.028
ACLF-1	35.2% (113/321)	0.00044	64.8% (390/602)	20.4% (21/103)	17.4% (63/363)	0.48	32.6% (31/95)	33.1% (111/335)	0.93
ACLF-2	48.9% (157/321)		26.7% (161/602)	35.9% (52/145)	34.9% (52/149)	0.87	54.8% (74/135)	54.8% (74/135)	1.0
ACLF-3	15.9% (51/321)	<0.0001	8.5% (51/602)	63.8% (30/47)	63.8% (30/47)	1.0	76.6% (36/47)	76.6% (36/47)	1.0
Alcohol-related	49.8% (160/321)		49.2% (296/602)	36.7% (54/147)	24.3% (68/280)	0.0068	51.5% (70/136)	38.7% (99/256)	0.015
ACLF-1	38.8% (62/160)	0.21	66.2% (196/296)	25.5% (14/55)	15.1% (28/186)	0.074	35.4% (17/48)	27.4% (46/168)	0.28
ACLF-2	45.6% (73/160)		25.3% (75/296)	39.7% (27/68)	38.6% (27/70)	0.89	56.3% (36/64)	56.3% (36/64)	1.0
ACLF-3	15.6% (25/160)	<0.0001	8.4% (25/296)	54.2% (13/24)	54.2% (13/24)	1.0	70.8% (17/24)	70.8% (17/24)	1.0
Autoimmune-related	13.7% (44/321)		17.6% (106/602)	21.7% (10/46)	24.7% (24/97)	0.69	45.5% (20/44)	44.6% (41/92)	0.92
ACLF-1	45.5% (20/44)	0.83	76.4% (81/106)	17.4% (4/23)	24.7% (18/73)	0.47	39.1% (9/23)	42.2% (30/71)	0.79
ACLF-2	47.7% (21/44)		20.8% (22/106)	20.0% (4/20)	19.0% (4/21)	0.94	50.0% (9/18)	50.0% (9/18)	1.0
ACLF-3	6.8% (3/44)	<0.0001	2.8% (3/106)	66.7% (2/3)	66.7% (2/3)	1.0	66.7% (2/3)	66.7% (2/3)	1.0
Others	36.4% (117/321)		34.2% (206/602)	38.1% (40/105)	29.9% (56/187)	0.16	53.0% (53/100)	48.9% (85/174)	0.51
ACLF-1	26.5% (31/117)	<0.0001	57.8% (119/206)	14.3% (4/28)	18.3% (20/109)	0.61	25.9% (7/27)	38.6% (39/101)	0.22
ACLF-2	53.8% (63/117)		31.1% (64/206)	36.8% (21/57)	36.2% (21/58)	0.94	54.7% (29/53)	54.7% (29/53)	1.0
ACLF-3	19.7% (23/117)	<0.0001	11.2% (23/206)	75.0% (15/20)	75.0% (15/20)	1.0	85.0% (17/20)	85.0% (17/20)	1.0

*P value for comparisons of the proportions of patients with ACLF-2 and patients with ACLF-1 or ACLF-3 under CLIF criteria.
†P value for comparisons of LT-free mortality between ACLF patients under CLIF criteria and those under COSSH criteria.
ACLF, acute-on-chronic liver failure; CLIF, chronic liver failure; COSSH, Chinese Group on the Study of Severe Hepatitis B; HBV, hepatitis B virus; LT, liver transplantation.

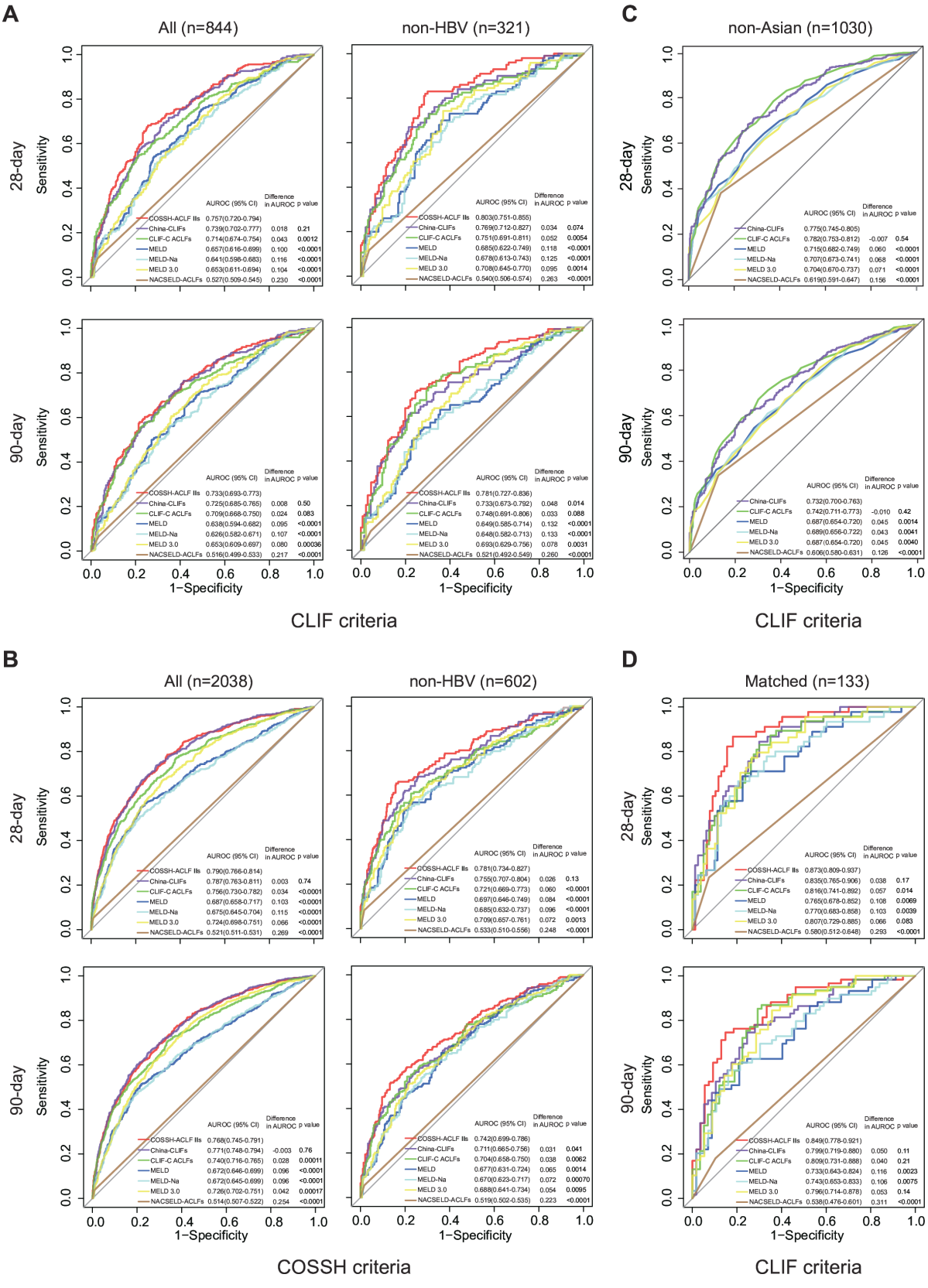

Figure 4 Receiver operating characteristic (ROC) curves for prognostic performance of seven scores at 28 and 90 days under CLIF and COSSH criteria. (A) In the derivation cohort under CLIF criteria; (B) In the derivation cohort under COSSH criteria; (C) In three non-Asian cohorts under CLIF criteria; (D) In matched ACLF patients with non-HBV aetiologies based on the frequency of six organ failures of the CANONIC cohort under CLIF criteria. ACLF, acute-on-chronic liver failure; AUROC, area under the ROC curve; China-CLIFs, China-Chronic Liver Failure score; CLIF-C ACLFs, CLIF Consortium ACLF score; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; HBV, hepatitis B virus; MELD, Model for End-Stage Liver Disease; MELD-Na, MELD-sodium; NACSELD-ACLFs, North American Consortium for the Study of End-Stage Liver Disease-ACLF score.

Table 3 Clinical characteristics of ACLF patients under CLIF criteria in the CANONIC, PREDICT and ACLARA cohorts

Characteristic	All (n=4072)	ACLF (n=1030)
Age (years)	57.6±12.0	55.7±12.5
Male (no.)	64.9% (2642)	65.0% (669)
Cirrhosis (no.)	100.0% (4072)	100.0% (1030)
Aetiology		
HBV-related	4.7% (190)	3.7% (38)
Non-HBV-related	95.3% (3882)	96.3% (992)
Alcohol-related	61.7% (2397)	63.6% (631)
Autoimmune-related	3.2% (124)	4.5% (45)
Parasite-related	NA	NA
Drug induced	NA	NA
HCV	19.0% (739)	16.2% (161)
Wilson's disease	0.3% (13)	0.5% (5)
MASLD	13.9% (564)	13.9% (138)
Undetermined	0.9% (37)	0.5% (5)
Complication		
HE	37.6% (1529)	61.6% (634)
GIH	20.0% (813)	18.0% (185)
Ascites	69.3% (2817)	79.6% (818)
Infection	34.5% (1404)	48.7% (502)
Laboratory data		
ALT (U/L)	32.0 (20.0–51.0)	35.0 (22.0–61.0)
AST (U/L)	57.0 (36.0–99.0)	70.0 (40.0–128.0)
ALP (U/L)	134.0 (91.0–203.0)	130.5 (89.0–204.0)
GGT (U/L)	86.0 (41.6–190.0)	77.0 (38.0–174.5)
Alb (g/L)	28.0 (24.0–32.3)	27.0 (23.0–32.0)
TB (μmol/L)	49.3 (25.0–116.5)	114.6 (35.9–307.8)
Creatinine (μmol/L)	88.4 (63.7–131.8)	187.9 (105.2–264.2)
Serum urea (mmol/L)	NA	NA
Sodium (mmol/L)	134.9±5.9	133.7±6.7
CRP (mg/L)	22.0 (9.5–47.0)	34.1 (17.6–66.5)
WCC (10^9/L)	6.4 (4.3–9.6)	9.0 (5.9–13.8)
Neutrophil (10^9/L)	4.3 (2.8–6.9)	6.9 (4.2–11.5)
Haemoglobin (g/L)	10.0 (8.6–11.6)	9.2 (8.1–11.0)
Haematocrit (%)	29.7 (25.4–34.0)	27.4 (23.9–32.2)
Platelet count (10^9/L)	93.0 (60.0–138.0)	88.7 (57.0–131.0)
INR	1.5 (1.3–1.9)	1.9 (1.5–2.6)
Severity score		
COSSH-ACLF IIs	NA	NA
China-CLIFs	NA	7.1 (6.3–8.1)
CLIF-C ACLFs	NA	50.4±10.7
MELD	18.9±7.8	27.8±7.2
MELD-Na	21.5±7.6	29.6±6.6
MELD 3.0	21.5±8.1	30.2±7.4
Organ failure		
Liver	14.1% (572)	39.4% (405)
Coagulation	9.6% (388)	30.7% (315)
Cerebral	8.4% (341)	24.2% (249)
Renal	14.9% (605)	58.4% (602)
Respiratory	3.6% (140)	12.8% (126)
Circulation	6.5% (261)	23.4% (240)
Transplant-free mortality		
28 days	14.5% (592)	38.9% (401)
90 days	24.2% (987)	50.3% (518)

Continued

Table 3 Continued

Characteristic	All (n=4072)	ACLF (n=1030)

A total of 4072 patients with acutely decompensated cirrhosis from three non-Asian cohorts were analysed for validation. Of these, 1030 patients were classified as ACLF based on the CLIF criteria. Categorical variables are expressed as percentages (n); continuous variables are expressed as either the mean±SD or median (Q1–Q3). ACLARA, Prevalence, Epidemiology, Characterization, and Mechanisms of Acute-on-Chronic Liver Failure in Latin America; ACLF, acute-on-chronic liver failure; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CANONIC, chronic liver failure consortium Acute-on-Chronic Liver Failure in Cirrhosis; CLIF-C, Chronic Liver Failure Consortium; COSSH, Chinese Group on the Study of Severe Hepatitis B; CRP, C reactive protein; GGT, glutamyl transferase; GIH, gastrointestinal haemorrhage; HE, hepatic encephalopathy; INR, international normalised ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; NA, not applicable; PREDICT, PREDICTing Acute-on-Chronic Liver Failure; TB, total bilirubin; WCC, white cell count.

might be categorised as 'acute decompensation' or 'acute severe liver injury in non-cirrhotic patients' under the CLIF criteria. However, they exhibited significant clinical severity and poor outcomes, as demonstrated in this study. Specifically, regardless of HBV or non-HBV aetiology, these patients primarily had liver-specific injury and a 28-day LT-free mortality rate exceeding the 15% cut-off value, accompanied by organ failure, which aligns with the features of the ACLF definition proposed by the CLIF

Table 4 Clinical characteristics of matched ACLF patients based on the frequency of organ failure of CANONIC cohort

Characteristic	Matched ACLF (n=133)	CANONIC (n=303)*
Age (years)	59±12	56±11
Male (no.)	68.7% (90)	64.4% (195)
Cirrhosis (no.)	100.0% (133)	100.0% (303)
Laboratory data		
ALT (U/L)	93±369	67±118
AST (U/L)	164±563	143±268
GGT (U/L)	111±117	141±160
TB (umol/L)	223±181	219±303
Creatinine (μmol/L)	206±134	203±141
Sodium (mmol/L)	136±8	133±6
Haematocrit (%)	25±7	29±6
Platelet count (10^9/L)	96±91	100±69
INR	2.1±1.0	2.1±0.9
Organ failure		
Liver	46.6% (62)	43.6% (132)
Coagulation	25.6% (34)	27.7% (84)
Cerebral	23.3% (31)	24.1% (73)
Renal	57.9% (77)	55.8% (169)
Respiratory	9.8% (13)	9.2% (28)
Circulation	17.3% (23)	16.8% (51)
Transplant-free mortality		
28 days	36.7% (47)	33.9% (95)
90 days	51.3% (61)	51.2% (134)

*The data from the original article of CANONIC study. To facilitate data comparison, the matched ACLF patients data were reported in a format consistent with the original data from the CANONIC study.
ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CANONIC, chronic liver failure consortium Acute-on-Chronic Liver Failure in Cirrhosis; GGT, glutamyl transferase; INR, international normalised ratio; TB, total bilirubin.

criteria. Furthermore, consistent with findings from previous studies,[3 8 24 25] this study also observed an unreasonable distribution of ACLF severity under CLIF criteria, with a high percentage of ACLF-2 patients (56.3%) regardless of HBV or non-HBV aetiology. In contrast, the COSSH criteria showed a more reasonable epidemiological pyramid-like distribution across severity grades (ACLF 1–3: 63.4%/27.5%/9.1%). The expanded capacity of the COSSH criteria to identify critically ill patients is reflected in their high LT-free mortality rates: 27.3% at 28 days and 41.0% at 90 days overall, with graded increases by severity (grade 1: 17.3%/30.5%; grade 2: 42.7%/58.6%; grade 3: 71.0%/79.8%). This is valuable in resource-limited settings, where accurate risk stratification is essential for prioritising interventions such as LT. The APASL criteria missed patients with extremely high mortality compared with the CLIF and COSSH criteria, as it focused on acute hepatotropic insults and excluded patients with prior decompensation. Patients identified exclusively by the APASL criteria had a <15% threshold 28-day LT-free mortality rate. These findings suggest that COSSH criteria more effectively identify high-risk patients, who have liver-specific injury or extrahepatic insults and may benefit from timely and intensive management. This may serve as a direction to adjust and complement the existing criteria by addressing their limitations in certain patient subgroups.

A simple and accurate prognostic score is crucial for making informed clinical decisions. MELD and MELD-Na are widely used to predict the mortality of patients with end-stage liver disease or for liver allocation; however, they may underestimate mortality in ACLF patients, as they only capture intrinsic liver disease.[28 29] MELD 3.0, an updated version of MELD-Na that incorporates sex and serum albumin as new variables, has not yet been validated in ACLF patients.[30] The APASL ACLF Research Consortium (AARC) score was applied to patients who were diagnosed as ACLF using the APASL criteria.[31] The NACSELD-ACLFs, positive if ≥2 organ failures are present, is a high-specificity bedside tool that predicts short-term mortality.[32] China-CLIFs and CLIF-C ACLFs, modified from the CLIF-OF scoring system, have been validated and used to predict short-term mortality in patients with HBV and non-HBV aetiologies, respectively.[8 20] COSSH-ACLF IIs was developed based on six predictors and was not constrained by a complex six-organ failure assessment system (15 parameters) that includes subjective factors, improving the prognostic ability and sensitivity of patients with ACLF of HBV aetiology.[20] Our recent study has revealed that the COSSH-ACLF IIs demonstrated higher prognostic efficiency than AARC score, CLIF-C ACLFs, MELD and MELD-Na for ACLF patients under APASL criteria (online supplemental table 11).[33] In this all-aetiology cohort, the comprehensive analysis revealed that the COSSH-ACLF IIs exhibited prognostic performance equivalent to the China-CLIFs for predicting the 28-day/90-day LT-free mortality, outperforming other scores. This finding applies not only to ACLF patients meeting COSSH criteria, but also to cirrhotic ACLF patients (both non-HBV and HBV aetiologies) meeting CLIF criteria. The clinical utility of COSSH-ACLF IIs was confirmed by risk stratification analysis in effectively categorising ACLF patients into three distinct mortality risk strata. The outperformance of these two scores likely stems from their comprehensive integration of liver-specific and extrahepatic indicators, along with the higher weight assigned to bilirubin—a key predictor of organ failure progression. This may also explain their applicability in non-cirrhotic patients, who probably present with distinct pathophysiological features and fewer extrahepatic organ failures, though their inclusion may increase the complexity in interpreting disease severity. External validation analysis in the CANONIC, PREDICT and ACLARA cohorts demonstrated that the China-CLIFs maintained robust prognostic performance even in non-HBV populations. Meanwhile, a mimic validation of COSSH-ACLF IIs, using a matching analysis of the frequency of six organ failures observed in the CANONIC cohort, similarly showed higher AUROC for 28-day LT-free mortality prediction compared with CLIF-C ACLFs and comparable performance for 90-day LT-free mortality in non-HBV patients. These findings demonstrated the China-CLIFs was a global tool validated across Asian and non-Asian populations. The COSSH-ACLF IIs emerged as a simplified alternative, making it easier to implement in clinical practice, but further prospective validation is needed in non-Asian cohorts.

We acknowledge several limitations in this study. First, the diagnostic bias may not be fully avoided due to regional variations in disease aetiologies, precipitating factors and socioeconomic determinants. Second, the assessment of scores at a single time point—without dynamic tracking (eg, over 48–72 hours)—limits our ability to validate their prognostic stability. Third, the risk stratification analysis partially relied on HRs, which are susceptible to built-in selection bias, potentially leading to biased estimates of risk.[34–36] Fourth, LT-free mortality was low (<15%) in non-cirrhotic patients with non-HBV aetiology, who comprised only 0.3% of all ACLF cases, indicating that COSSH-ACLF IIs and China-CLIFs should be applied with caution in this subgroup. Finally, the mimic validation within the derivation dataset did not account for differences in healthcare systems, treatment strategies or diagnostic practices. It focused on organ failure distribution, excluding other variables, which may lead to residual confounding. Therefore, the broader validation of the COSSH-ACLF IIs across diverse regions, countries and populations, including MASLD cohorts, is needed to confirm its generalisability.

Harmonising the definition of ACLF is achievable through collaboration. Future efforts should prioritise establishing a multinational working group, grounded in prospective, validated data, to unify core diagnostic elements—such as organ failure criteria and the chronic liver disease basis—while allowing adaptation to regional aetiologies and healthcare conditions. The definition should incorporate shared characteristic pathological features and key pathophysiological mechanisms across diverse aetiologies.[10] Integrating multiomics profiling would facilitate a biologically driven classification of ACLF subtypes, enhancing diagnostic precision and guiding personalised therapy.[37] Integrating validated prognostic elements from existing scoring systems into a unified dynamic-assessment model could enable global outcome comparability and accelerate international clinical research.

In summary, the China-CLIF framework—integrating elements of the COSSH and CLIF criteria—bridges gaps between Asian and non-Asian cohorts by balancing sensitivity (early diagnosis) and specificity (multiorgan failure recognition). This framework demonstrates broader applicability across diverse aetiologies and geographic regions compared with existing systems. Our findings provide a valuable foundation for harmonising ACLF definitions, a critical step towards reducing global disparities in ACLF management and advancing therapeutic research.

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