




ORIGINAL ARTICLE

Acute-on-chronic liver failure: Epidemiology, prognosis, and outcome of a multicenter study in Thai population

Sakkarin Chirapongsathorn,*  Tongluk Teerasartipan,[†]  Krit Tipchaichatta,* Tanita Suttichaimongkol,[‡]  Naichaya Chamroonkul,[§] Chalermrat Bunchorntavakul,[¶] Sith Siramolpiwat,^{||} Siwaporn Chainuvati,** Abhasnee Sobhonslidsuk,^{††} Apinya Leerapun,^{‡‡} Teerha Piratvisuth,[§] Wattana Sukeepaisarnjaroen,[‡] Tawesak Tanwandee** and Sombat Treeprasertsuk[†]

*Division of Gastroenterology, Phramongkutklao Hospital and College of Medicine, [†]Department of Medicine, Division of Gastroenterology, Faculty of Medicine, Chulalongkorn University and Thai Red Cross, [‡]Division of Gastroenterology and Hepatology, Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, [§]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Thammasat University, **Division of Gastroenterology, Department of Medicine, Siriraj Hospital, ^{††}Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok, ^{‡‡}Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, [§]Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla and ^{¶¶}Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand

Key words

acute-on-chronic liver failure, cirrhosis, organ failure.

Accepted for publication 10 February 2022.

Correspondence

Sombat Treeprasertsuk, Chulalongkorn University, 254 Phayathai Street, Pathum Wan, Pathum Wan District, Bangkok 10330, Thailand.
Email: sombat.t@chula.ac.th

Declaration of conflict of interest: None.

Author contribution: Sakkarin Chirapongsathorn contributed to the review of data for eligibility, evaluation of quality and data extraction; writing the manuscript, data analysis, authorship. Tongluk Teerasartipan contributed to the review of data for eligibility and data extraction, evaluation of quality. Krit Tipchaichatta contributed to the review of data for eligibility and data extraction, drafting the manuscript. Tanita Suttichaimongkol, Naichaya Chamroonkul, Chalermrat Bunchorntavakul, Sith Siramolpiwat, Siwaporn Chainuvati, Abhasnee Sobhonslidsuk, and Apinya Leerapun contributed to the data extraction. Teerha Piratvisuth, Wattana Sukeepaisarnjaroen, and Tawesak Tanwandee contributed to the supervising and study concept. Sombat Treeprasertsuk contributed to the content expertise, study concept, supervisor, and authorship.

Financial support: This study was funded and supported by a research grant from the Thai Association for the Study of the Liver (THASL), Department of Medicine, Phramongkutklao Hospital, and Fatty Liver Fund, Foundation of Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Abstract

Background and Aim: Acute-on-chronic liver failure (ACLF) leads to multi-organ failure related to high mortality rates. This study aimed to gather epidemiological data and validate a scoring system to predict mortality in ACLF.

Methods: This retrospective cohort study collected data from multicenter tertiary care hospitals in Thailand. A total of 638 hospitalized patients (acute decompensated liver disease [ADLD], 292 patients; ACLF, 346 patients) from January 2019 to June 2020 were enrolled in this study. We compared the mortality rate at days 30 and 90 between patients with ADLD and ACLF. Areas under the receiver operating characteristic (AUROC) curves of chronic liver failure–sequential organ failure assessment (CLIF-SOFA) and other existing scoring systems were compared among patients with ACLF.

Results: The incidence of patients with ACLF was 54%. The main cause of chronic liver disease was alcohol (38%), with sepsis (50%) as the most common precipitating factor. ACLF with coagulopathy (AUROC 0.58, 95% confidence interval [CI]: 0.52–0.64), metabolic acidosis (AUROC 0.58, 95% CI: 0.52–0.64), and high aspartate aminotransferase (AST) (AUROC 0.59, 95% CI: 0.53–0.66) were associated with high 30-day mortality. The 30-day mortality rate of patients with acute decompensation and patients with ACLF was 46 and 58%, respectively. Respiratory system ($P = 0.001$) failure was the major end result in ACLF and constituted a significant factor to predict mortality. The AUROC of CLIF-SOFA score was superior to that of the other predicted score (AUROC 0.64, 95% CI: 0.585–0.704).

Conclusion: Patients with ACLF with more organ failure and high CLIF-SOFA score were associated with high short-term mortality. Future studies should include an ACLF prospective registry to confirm these findings.

Funding support: Thai Association for the Study of the Liver (THASL), Fatty Liver Fund, Foundation of Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, and from Department of Medicine, Phramongkutklao Hospital, Royal Thai Army, Bangkok, Thailand

Introduction

Acute-on-chronic liver failure (ACLF) is the condition where acute decompensated liver function is aggravated by precipitating factors in patients with cirrhosis. Acute decompensation (AD) is associated with organ failure(s) including declining liver function, kidney failure, coagulopathy, and/or failure of other organs. Patients with ACLF are at high risk of short-term mortality. Related studies have provided information about ACLF epidemiology, burden of the disease, and outcomes of patients with ACLF.¹ However, these studies have been conducted in different countries and with possibly limited generalizability to patients seen outside their center. Targeting ACLF is a proposed priority of the national health policy.

We conducted the first multicenter study in Thailand aimed at determining the prevalence of ACLF in the tertiary medical center network in Thailand and short-term mortality among patients with decompensated cirrhosis admitted to hospitals.

Methods

Study populations. This retrospective study using patient registry was performed among patients with cirrhosis hospitalized with acute decompensation (AD) in multicenter tertiary care hospitals in Thailand (nine hospitals) from January 2019 to June 2020. Patients were included if they met the following criteria: (i) Thai nationals with age greater than 18 years; (ii) the presence of cirrhosis as diagnostic sign from clinical, biochemical, radiologic, endoscopic, or histopathologic results from any causes; (iii) hospitalized due to AD of the liver, and (iv) admitted between January 2019 and June 2020. Patients were excluded if they had the following conditions: (i) chronic kidney disease as defined by the KDOQI guidelines (glomerular filtration rate; [GFR] < 60 mL/min/1.73 m² for 3 months, or kidney damage [functional or structural abnormalities] for more than 3 months); (ii) hospitalized and scheduled for treatment or procedure; (iii) severe chronic extrahepatic disease; (iv) receiving immunosuppressive drugs for causes other than severe alcoholic hepatitis, and (v) pregnant. This study used individual retrospective administrative claims data. Data were de-identified and comply with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Human Research Ethics Committee (HREC) of all the participating centers. Informed consent was waived, as the data were retrospectively retrieved and analyzed in a de-identified format, and the case record form was also approved by the HREC of all participating centers. The members of the writing committee assumed responsibility for the accuracy and completeness of the data and for the fidelity of the study to the protocol. All authors

had access to the study data and reviewed and approved the final manuscript.

ACLF was diagnosed according to the EASL-CLIF Consortium (CANONIC study) by the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score or according to the APASL ACLF research consortium (AARC) by the AARC score.^{1,2} The EASL-CLIF Consortium identified failures of the liver, coagulation, kidney, circulation, lungs, and cerebral systems. Concisely, the definition of organ failure uses a modified SOFA score, namely the CLIF-SOFA score (Table S1, Supporting information). Patients who had one organ failure with the presence of declined kidney function (creatinine 1.5–1.9 mg/dL) or mild-to-moderate hepatic encephalopathy,³ single kidney failure and more than two organ failures were diagnosed as suffering from ACLF. ACLF was categorized into three grades, namely 1, 2, and 3, according to the EASL-CLIF Consortium definition.¹ The AARC score includes subscores ranging from 1 to 3 for each of five components (total bilirubin, hepatic encephalopathy grade, INR, creatinine levels, and blood lactate levels). Aggregated scores range from 5 to 15, with higher scores indicating more severe ACLF.⁴ In our study, we did not have the treatment protocol consensus by the investigators. However, all investigators followed management of ACLF in the ICU, related to EASL-CLIF Consortium and/or APASL ACLF research consortium recommendations.

Primary outcome and data collection. The primary outcome was transplant-free mortality within 30 and 90 days after collecting the data on admissions for decompensated cirrhosis. The clinical and laboratory data were collected, including age, sex, cause of cirrhosis, comorbidity, precipitating events, laboratory information, events of organ failures, and time to death. The precipitating events that directly or indirectly affected hepatocytes such as alcohol consumption, acute exacerbation of hepatitis B virus, drug-induced liver injury, bacterial infection, or upper gastrointestinal bleeding were collected. All variables of data used to analyze all models were collected at the onset of ACLF. Prognostic models used in anticipating the time-dependent death of patients with ACLF were Child-Turcotte-Pugh score (CTP), model for end-stage liver disease (MELD), MELD-sodium (MELD-Na), chronic liver failure-sequential organ failure assessment (CLIF-SOFA), chronic liver failure-organ failure (CLIF-OF), and chronic liver failure-consortium (CLIF-C).

The CTP score (range: 5–15) was computed by hepatic encephalopathy, ascites, serum albumin, serum bilirubin, and INR.⁵ The MELD score (range: 6–40) was calculated as $9.6 \times \log(\text{creatinine [mg/dL]}) + 3.8 \times \log(\text{bilirubin [mg/dL]}) + 11.2 \times \log(\text{INR}) + 6.43$.⁶ The MELD-Na score was adjusted based on the MELD score and calculated as follows: $\text{MELD-Na} = \text{MELD-Na} - [0.025 \times \text{MELD} \times (140 - \text{Na})] + 140$,

where the serum sodium concentration (Na) is bound between 125 and 140 mmol/L. Similar to the MELD score, the MELD-Na score is rounded to the nearest integer.⁷ The CLIF-SOFA score (range: 0–24) was computed by the sum of scores for six organ systems, comprising the liver, coagulation, respiratory, cardiovascular, renal, and nervous systems. The CLIF-C OF score was calculated by the sum of the modified six organ systems of the CLIF-SOFA score. The CLIF-C score was modified based on the CLIF-C OF score and calculated as follows: $10 \times [0.33 \times \text{CLIF-C OF} + 0.04 \times \text{age} + 0.63 \times \log(\text{white cell count}) - 2]$.¹ The AARC score (range: 5–15), determined by five variables (total bilirubin, creatinine, serum lactate, hepatic encephalopathy, and INR), was calculated, and patients were divided in three grades: Grade A (score 5–7), Grade B (score 8–10), and Grade C (score 11–15).^{4,8}

Statistical analysis. Data were collected using an electronic case record form. According to incidence of ACLF from the CANONIC study (22%), the sample size of our study was 374 (adding 10% lost to follow-up). Continuous variables are shown as mean \pm SD or interquartile range and categorical variables as percentage. Statistical analyses were performed using the chi-square or Fisher's exact test for categorical variables and the Mann–Whitney test for continuous variables. The statistical significance was defined at a *P*-value <0.05 . We used the SPSS Software, version 26.0 (SPSS Inc., Chicago, IL, USA) to analyze the data.

Results

Baseline demographic data and prevalence of ACLF in the tertiary medical center network. We identified 638 patients hospitalized for more than 24 h with an episode of decompensated cirrhosis from January 2019 to June 2020 with acute decompensated liver disease (ACLD) in nine multicenter tertiary care hospitals in Thailand; 346 patients (54%) presented with clinical conditions eligible to classify them as ACLF and 292 patients (46%) presented with only AD. Patients with AD had fewer laboratory signs indicating organ failures than those with ACLF (Table 1). Among patients presenting ACLF, those meeting the criteria for ACLF comprised grade 1 ACLF (31%), grade 2 ACLF (37%), and grade 3 ACLF (32%).

Baseline demographic data and laboratory results of patients with AD and ACLF are summarized in Table 1. In this study, the main study population was male (66%), and the average age was 58 ± 13.9 years. Among patients with ACLF, the etiologies of cirrhosis included alcohol consumption (38%), hepatitis B (17%), hepatitis C (12%), non-alcoholic steatohepatitis (NASH), and others (21%). The main precipitating factors among patients with ACLF included sepsis (50%), gastrointestinal bleeding (21%), spontaneous bacterial peritonitis (14%), and alcohol consumption (12%). Patients with ACLF had a significantly higher white blood cell count ($10.48 \times 10^9/\text{L}$ vs $8.56 \times 10^9/\text{L}$; $P < 0.001$), higher INR (1.82 vs 1.41; $P < 0.001$), higher aspartate aminotransferase (AST) (117 vs 62 U/L; $P < 0.001$), and lower bicarbonate level (18 vs 21 mEq/dL).

Mortality of ACLF. Three-hundred and thirty-three (52%) patients died within 30 days and 409 (64%) within 90 days. The 30-day mortality was higher among patients with ACLF than those with AD (58 vs 46%, $P < 0.001$) (Table 1). The risk of 30-day mortality increased with the severity of ACLF. Grade 2 and grade 3 ACLF had similar risk of 30-day mortality. At 90 days, mortality was higher among patients with ACLF than among patients with AD (70 vs. 57%, $P < 0.001$). A similar trend was observed in that increasing the grade of organ failures resulted in an increase in 90-day mortality in the ACLF group (Table 2). The overall mortality rate of AD and ACLF at 30 days and 90 days were 52 and 64%, respectively. Patients with ACLF and coagulopathy (AUROC 0.58, 95% confidence interval [CI]: 0.52–0.64), metabolic acidosis (AUROC 0.58, 95% CI: 0.52–0.64), and high AST (AUROC 0.59, 95% CI: 0.53–0.66) were associated with high 30-day mortality. Respiratory system ($P = 0.001$) failure was the major event in ACLF that significantly predicted mortality. Figures 1 and 2 show the comparisons of the ROC curves for 30-day and 90-day mortality at admission by INR, AST, serum bicarbonate, and medical scores.

Prognostic factors for mortality among patients with ACLF. Table 2 summarizes the clinical factors associated with 30- and 90-day mortality among patients with ACLF. Coagulopathy and worsening of renal and respiratory functions, decompensation of liver function, and hepatic encephalopathy were significantly associated with 30-day mortality. All prognostic scores (MELD, MELD-Na, CLIF-SOFA, CLIF-OF, and CLIF-C) were significantly higher in 30-day and 90-day mortality. In all grades of ACLF, kidney failure was the most common cause of death among patients. Low bicarbonate level ($P = 0.011$), high AST level ($P = 0.005$), and high INR level ($P = 0.013$) correlated with 30-day mortality.

Comparison between prognostic models. Tables 3 and 4 show the comparisons of AUROC between six prognostic models, namely MELD, MELD-Na, CLIF-SOFA, CLIF-OF, CLIF-C, and ACLF grading by CLIF-SOFA. The AUROC of CLIF-SOFA for 30-day mortality was significantly better than for other prognostic models (0.64, 95% CI: 0.59–0.70; $P < 0.001$). Chronic liver failure–sequential organ failure assessment (CLIF-SOFA) score ≥ 12 and model for end-stage liver disease-sodium (MELD-Na) score >30 were associated with high mortality rates. The AUROC of the CLIF-SOFA score was superior to those of other predicted scores.

Discussion

We report three major findings among patients with cirrhosis admitted with hepatic decompensation in multicenter tertiary care hospitals in Thailand. First, ACLF was present among 54% of patients admitted with decompensated cirrhosis. The most common underlying predisposing liver disease in ACLF was alcohol consumption (38%), whereas bacterial sepsis (50%) and gastrointestinal bleeding (21%) were identified as major predisposing factors for ACLF. Second, nearly one-half of these patients (55%) died within 30 days of admission and almost 65% died within 90 days. The presence of two or more organ failures, defined by the ACLF grade by CLIF-SOFA, was associated with

30- and 90-day mortality. Third, presenting acidosis, prolonged INR, and high AST level were associated with mortality among patients with ACLF.

ACLF was more common in our population (54 vs 23%) than the related original cohort in the CANONIC study.¹ This implicates a referral bias because all subjects enrolled in our

Table 1 Baseline demographic data of acute decomposition (AD) and acute-on-chronic liver failure (ACLF)

Characteristic	Total (n = 638)	AD (n = 292)	ACLF (n = 346)	P value
Sex				
Male	420 (66%)	190 (65%)	230 (67%)	0.709
Female	218 (34%)	102 (35%)	116 (33%)	
Age	58 ± 13.9	59 ± 13.4	58 ± 14.3	0.244
Precipitating factors				
Sepsis	267 (42%)	95 (33%)	172 (50%)	<0.001*
Gastrointestinal bleeding	197 (31%)	124 (43%)	73 (21%)	<0.001*
Spontaneous bacterial peritonitis	72 (11%)	24 (8%)	48 (14%)	0.025*
Alcoholic consumption	52 (8%)	10 (3%)	42 (12%)	<0.001*
Cause of chronic liver disease				
Alcohol	247 (39%)	114 (39%)	133 (38%)	0.876
Hepatitis B	95 (15%)	38 (13%)	57 (17%)	0.221
Hepatitis C	95 (15%)	52 (18%)	43 (12%)	0.057
Hepatitis B + alcohol	23 (4%)	8 (3%)	15 (4%)	0.281
Hepatitis C + alcohol	29 (6%)	12 (4%)	17 (5%)	0.627
NASH and others	149 (21%)	68 (23%)	81 (24%)	0.328
Na ⁺ (mEq/dL)	133 ± 7.11	134 ± 5.87	132 ± 7.86	<0.001*
Hemoglobin (g/dL)	9.7 ± 3.49	9.6 ± 4.41	9.7 ± 2.48	0.744
Hematocrit (%)	29.2 ± 11.01	28.7 ± 8.08	29.5 ± 12.99	0.391
White blood cell (×10 ⁹ /L)	9.50 (6.24, 14.05)	8.56 (5.43, 12.45)	10.48 (6.88, 15.80)	<0.001*
Platelet (×10 ⁹ /L)	108 (70, 164)	108 (71, 167)	109.5 (68, 164)	0.656
INR	1.6 (1.34, 2.11)	1.41 (1.28, 1.68)	1.82 (1.5, 2.5)	<0.001*
BUN (mg/dL)	22 (13, 37.5)	18 (11, 28)	29 (14.9, 45.3)	<0.001*
Creatinine (mg/dL)	1.11 (0.78, 1.87)	0.9 (0.7, 1.19)	1.65 (0.93, 2.49)	<0.001*
HCO ₃ ⁻ (mEq/dL)	19.3 ± 6.59	21 ± 6.72	17.86 ± 6.13	<0.001*
Total bilirubin (mg/dL)	3.6 (1.6, 10.45)	2 (1.18, 4.21)	7.1 (2.82, 17.1)	<0.001*
Direct bilirubin (mg/dL)	2.3 (0.9, 6.9)	1.19 (0.63, 2.41)	4.76 (1.9, 12.01)	<0.001*
AST (U/L)	88.05 (48, 174)	62 (39, 124)	117.25 (61, 224)	<0.001*
ALT (U/L)	39 (23, 69)	32 (20, 51)	46 (28, 84)	<0.001*
Alkaline phosphatase (U/L)	125 (90, 182)	121 (86.5, 167.5)	129 (92, 191)	0.077
Albumin (g/dL)	2.5 (2.1, 3)	2.7 (2.3, 3.1)	2.4 (2, 2.9)	<0.001*
Hepatic encephalopathy				
1	357 (56%)	283 (96.7%)	38 (10%)	<0.001*
2	89 (14%)	4 (1.5%)	85 (25%)	
3	103 (16%)	1 (0.3%)	120 (35%)	
4	89 (14%)	4 (1.5%)	103 (30%)	
Child–Turcotte–Pugh	10 (8, 12)	9 (7, 11)	11 (10, 13)	<0.001*
Status at 30th day				
Alive	305 (48%)	159 (54%)	146 (42%)	0.001*
Dead	333 (52%)	133 (46%)	200 (58%)	
Status at 90th day				
Alive	229 (36%)	125 (43%)	104 (30%)	<0.001*
Dead	409 (64%)	167 (57%)	242 (70%)	
CLIF-OF	10 ± 2.33	8 ± 1.46	11 ± 2.18	<0.001*
CLIF-C	49 ± 10.75	43 ± 8.76	54 ± 9.99	<0.001*
CLIF-SOFA	9 ± 3.75	7 ± 2.45	11 ± 3.28	<0.001*
Total AARC	9 ± 2.03	8 ± 1.42	10 ± 1.86	<0.001*
MELD	22 ± 9.31	16 ± 6.24	27 ± 8.58	<0.001*
MELD-Na	24 ± 8.51	19 ± 6.27	29 ± 7.45	<0.001*

Value presented as mean ± SD or median (interquartile range) and *n* (%). *P* value corresponds to independent *t*-test or the Mann–Whitney test and chi-square test.

*The significance of *P* < 0.05.

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C, chronic liver failure-consortium; CLIF-OF, chronic liver failure-organ failure CLIF-SOFA, chronic liver failure–sequential organ failure assessment; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.

study were from tertiary care centers. Moreover, the short-term mortality in our study was also higher than that in the CANONIC study (55% died within 30 days vs 34% within 28 days). We believe the difference was due to demographic factors (age,

race), socioeconomic status, and underlying liver disease, especially chronic hepatitis B infection. Moreover, almost all of our patients with ACLF were involved with bacterial infection (sepsis, gastrointestinal bleeding, and spontaneous bacterial

Table 2 Prognostic factors for 30- and 90-day mortality in patients with acute-on-chronic liver failure

Characteristic	30-day mortality			90-day mortality		
	Alive (n = 146)	Dead (n = 200)	P value	Alive (n = 104)	Dead (n = 246)	P value
Sex						
Male	96 (66%)	136 (68%)	0.914	67 (64%)	160 (65%)	0.791
Female	50 (34%)	64 (32%)		37 (36%)	86 (35%)	
Age	57 ± 14.76	59 ± 13.57	0.104	56 ± 14.14	59 ± 13.57	0.010*
Child–Turcotte–Pugh	11 (9, 13)	12 (10, 13)	0.821	11 (8, 12)	12 (10, 13)	0.775
Na ⁺ (mEq/dL)	133 (129, 135)	132 (127, 137)	0.806	133 (129, 136)	132 (127, 137)	0.396
Hemoglobin (g/dL)	9.8 (7.9, 11.5)	10 (8.1, 11.2)	0.953	9.8 (7.55, 11.8)	10 (8.1, 11.2)	0.923
Hematocrit (%)	29.2 (23.1, 34.4)	29.1 (24.3, 33.4)	0.906	29.2 (22.75, 35)	29.1 (24.3, 33.3)	0.957
White blood cell (×10 ⁹ /L)	10.11 (6.9, 15.33)	11.11 (6.84, 16.50)	0.367	10.84 (6.92, 15.74)	10.46 (6.70, 15.8)	0.884
Platelet (×10 ⁹ /L)	107 (73, 156)	111 (61, 164)	0.822	103.5 (73, 155)	112 (65, 173)	0.765
INR	1.76 (1.47, 2.25)	1.95 (1.52, 2.74)	0.013*	1.76 (1.48, 2.22)	1.93 (1.5, 2.6)	0.097
BUN (mg/dL)	23 (13, 39)	31 (17.5, 53)	0.001*	23 (13, 39.5)	31 (17, 51)	0.009*
Creatinine (mg/dL)	1.46 (0.86, 2.34)	1.8 (1, 2.69)	0.024*	1.56 (0.895, 2.37)	1.73 (0.97, 2.6)	0.276
HCO ₃ ⁻ (mEq/dL)	19 (16, 22)	17.1 (13, 21)	0.011*	18.5 (16, 22)	17.6 (13.3, 21.3)	0.213
Total bilirubin (mg/dL)	5.9 (2.48, 15.23)	7.8 (3.2, 17.1)	0.087	6.6 (2.77, 17.75)	7.1 (2.83, 15.39)	0.762
Direct bilirubin (mg/dL)	4 (1.65, 11)	5.67 (2.2, 12.6)	0.037*	4.3 (1.57, 11.75)	4.9 (2, 11.6)	0.360
AST (U/L)	103 (57, 175)	143 (68, 307)	0.005*	110 (57.5, 178)	122 (66, 266)	0.122
ALT (U/L)	41 (27, 72)	53 (31, 109)	0.005*	42 (27.5, 77)	50 (30, 93)	0.085
Alkaline phosphatase (U/L)	129 (91, 189)	130 (92, 197)	0.678	117 (87, 187)	133 (93, 198)	0.166
Albumin (g/dL)	2.4 (2, 3)	2.4 (2.1, 2.9)	0.836	2.4 (2, 3.05)	2.4 (2.07, 2.8)	0.482
Hepatic encephalopathy						
1	27 (18%)	19 (10%)	0.007*	20 (19%)	29 (12%)	0.028*
2	43 (29%)	48 (24%)		32 (31%)	61 (25%)	
3	44 (30%)	65 (33%)		30 (29%)	79 (32%)	
4	32 (23%)	65 (33%)		22 (21%)	77 (31%)	
CLIF-OF	10 (9, 11)	11 (10, 13)	<0.001*	10 (9, 11)	11 (9, 12.5)	0.008*
CLIF-C	51 (45, 57)	55 (49, 62)	<0.001*	51 (46, 56)	55 (47, 62)	0.001*
MELD	24 (19.81, 29.74)	28 (21.46, 33.79)	0.001*	24 (20.07, 29.62)	27 (20.32, 33.32)	0.069
MELD-Na	28 (22.47, 32.31)	30 (24.33, 35.22)	0.001*	28 (22.59, 32.31)	30 (23.32, 34.82)	0.035*
Organ failure						
Liver	49 (34%)	71 (37%)	0.470	38 (37%)	79 (35%)	0.845
Kidney	50 (34%)	80 (42%)	0.143	36 (35%)	89 (40%)	0.359
Cerebral	38 (26%)	65 (34%)	0.107	27 (26%)	74 (33%)	0.188
Coagulation	28 (19%)	57 (30%)	0.024*	20 (19%)	62 (28%)	0.096
Circulation	52 (36%)	72 (38%)	0.668	39 (38%)	83 (37%)	0.961
Lung	25 (17%)	69 (36.3%)	<0.001*	17 (16%)	76 (34%)	0.001*
Total CLIF-SOFA	10 (8, 13)	12 (10, 15)	<0.001*	10 (8, 13)	11 (9, 14)	0.001*
ACLF grade by CLIF-SOFA						
Grade 0	32 (22%)	19 (9%)	0.003*	20 (19%)	29 (12%)	0.082
Grade 1	43 (30%)	45 (23%)		33 (32%)	52 (21%)	
Grade 2	42 (28%)	68 (34%)		30 (29%)	84 (34%)	
Grade 3	29 (20%)	68 (34%)		21 (20%)	81 (33%)	
ACLF grade by AARC						
Grade 1	43 (30%)	44 (23%)	0.058	33 (32%)	52 (23%)	0.090
Grade 2	42 (29%)	62 (33%)		30 (29%)	71 (32%)	
Grade 3	29 (20%)	62 (33%)		21 (20%)	68 (31%)	
Total AARC	9.8 ± 1.72	10.5 ± 1.9	0.005*	9.9 ± 1.68	10.3 ± 1.92	0.161

*The significance of $P < 0.05$.

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C, chronic liver failure-consortium; CLIF-OF, chronic liver failure-organ failure; CLIF-SOFA, chronic liver failure–sequential organ failure assessment; MELD, model for end-stage liver disease.

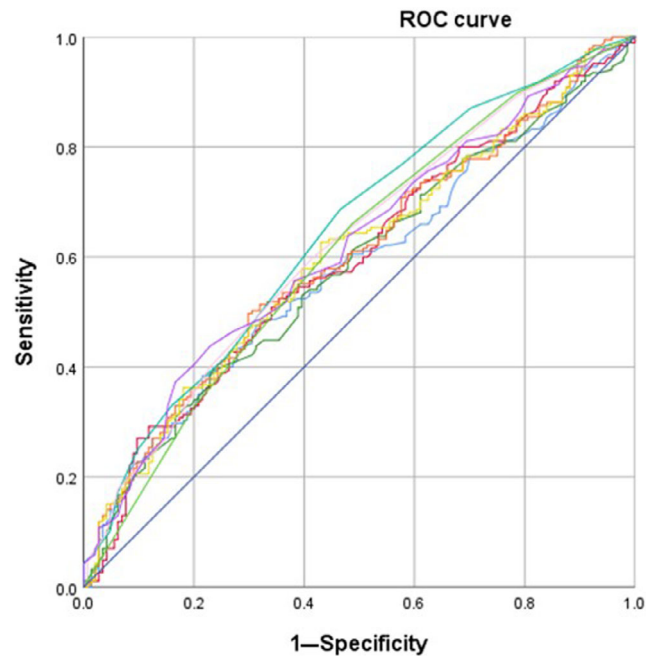


Figure 1 Comparisons of the receiver operating characteristic (ROC) curves for 30-day mortality at admission by INR, aspartate aminotransferase (AST), serum bicarbonate, and medical scores. Source of the curve: (—), INR; (—), AST; (—), HCO_3^- ; (—), MELD; (—), MELD-Na; (—), chronic liver failure (CLIF)–sequential organ failure assessment; (—), CLIF-OF; (—), CLIF-C; (—), ACLF grade by CLIF-SOFA; (—), reference line.

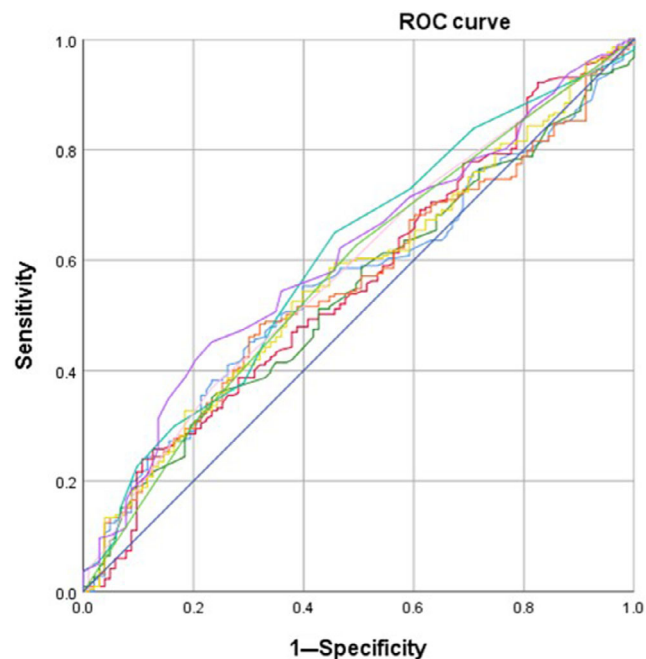


Figure 2 Comparisons of the receiver operating characteristic (ROC) curves for 90-day mortality at admission by INR, aspartate aminotransferase (AST), serum bicarbonate, and medical scores. Source of the curve: (—), INR; (—), AST; (—), HCO_3^- ; (—), model for end-stage liver disease (MELD); (—), MELD-Na; (—), CLIF-SOFA; (—), CLIF-OF; (—), CLIF-C; (—), ACLF grade by CLIF-SOFA; (—), reference line

infection). Bacterial infection is a well-known precipitating factor of organ failure and ACLF among patients with cirrhosis. Studies have shown that the in-hospital mortality and 28-day mortality in Asia are higher than in America and Europe.^{4,9} Patients

developing ACLF in Asia more often had infection frequently caused by multidrug or extensively drug-resistant bacteria.^{10,11} All these factors may have contributed to the variations in the epidemiology and outcomes of ACLF in different areas globally.

Table 3 Areas under the receiver operating characteristic (AUROC) curves of prognostic models to predict 30-day mortality

Test result variable(s)	AUROC	Std. error [†]	P value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
INR	0.58	0.031	0.012	0.519	0.642
AST	0.59	0.031	0.003	0.533	0.656
HCO ₃ ⁻	0.58	0.031	0.012	0.519	0.642
MELD	0.60	0.031	0.002	0.539	0.661
MELD-Na	0.60	0.031	0.002	0.541	0.662
CLIF-SOFA	0.64	0.030	<0.001	0.585	0.704
CLIF-OF	0.62	0.031	<0.001	0.563	0.684
CLIF-C	0.62	0.031	<0.001	0.557	0.678
ACLF grade by CLIF-SOFA	0.61	0.031	0.001	0.549	0.672
ACLF grade by AARC	0.597	0.037	0.01	0.525	0.669

[†]The significance of $P < 0.05$.

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; AST, aspartate aminotransferase; CLIF-C, chronic liver failure-consortium; CLIF-OF, chronic liver failure-organ failure; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; MELD, model for end-stage liver disease.

Table 4 Areas under the receiver operating characteristic (AUROC) curves of prognostic models to predict 90-day mortality

Test result variable(s)	AUROC	Std. error [†]	P value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
INR	0.56	0.033	0.093	0.493	0.623
AST	0.56	0.034	0.094	0.491	0.625
HCO ₃	0.54	0.033	0.226	0.476	0.607
MELD	0.56	0.033	0.113	0.490	0.620
MELD-Na	0.57	0.033	0.053	0.501	0.632
CLIF-SOFA	0.61	0.033	0.002	0.541	0.672
CLIF-OF	0.59	0.033	0.014	0.519	0.651
CLIF-C	0.61	0.033	0.002	0.544	0.673
ACLF grade by CLIF-SOFA	0.58	0.034	0.022	0.513	0.646
ACLF grade by AARC	0.561	0.040	0.141	0.483	0.639

[†]The significance of $P < 0.05$.

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; AST, aspartate aminotransferase; CLIF-C, chronic liver failure-consortium; CLIF-OF, chronic liver failure-organ failure; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; MELD, model for end-stage liver disease.

However, the precipitating factor in our study is sepsis in nearly half, and is missing some entities such as drug-induced liver injury, hepatitis B reactivation, and autoimmune hepatitis flare. It may be due to referral bias or not actual presentation of registry data. In our study, we used the CLIF-SOFA score to identify patients with ACLF. Patients with AD had fewer features related to organ failure than those with ACLF. However, in our cohort, patients with AD were still at risk of short-term mortality because most patients were admitted to hospitals due to critical illness conditions (sepsis and gastrointestinal bleeding). Although patients with cirrhosis admitted with AD had not developed ACLF, these patients should also be targeted to provide strategies to improve their survival. We also found that the AARC score could also be used to differentiate patients with ACLF. However, we encountered limitations in using the AARC score because it included the lactate level at admission, which was inapplicable in routine practice to every patient from our centers.

The presence of organ failure was strongly related to the patients' short-term mortality. Active alcohol consumption, alcoholic hepatitis, and bacterial infection were the most frequent factors

precipitating the development of ACLF in alcohol liver disease.¹² The specific clinical and pathologic features are related to presenting systemic and hepatic inflammation.¹² In our study, patients who were active alcohol consumers tended to develop ACLF more frequently than those who were nondrinkers or reported absolute abstinence.

Many models and laboratory features may predict the prognosis of ACLF. As the ACLF grades increased, the survival rates decreased. We cross-validated the diagnostic performances for short-term mortality among models and found that the AUROCs of the CLIF-SOFA, CLIF-OF, and CLIF-C scores showed a modest effect to predict short-term mortality and CLIF-SOFA, CLIF-OS, and CLIF-C were similar to MELD and MELD-Na. However, our study found that all prognostic variables had lower AUROC to predict mortality than in the related Asian cohort.¹¹ To explain this result, our cohort had higher short-term and long-term mortality. It could have resulted from using a model to validate severe cirrhotic cases of those admitted in tertiary care centers. The diagnostic performances among those models may have been lower.

Our study had some limitations. First, this study was conducted using a retrospective cohort, which could lead to selection bias

and their retrospective nature of data. Second, all subjects enrolled in our study were from tertiary care centers in Thailand, which also could lead to a referral bias and may not be generalizable to other areas in the healthcare system. Third, we had limited access to investigate data concerning artificial liver support, which may have altered our cohort outcome. However, the volume to use artificial liver support is very limited to access in our country. Finally, we could not validate the diagnostic performance of the AARC score because we lacked data on the lactate level.

In conclusion, hospitalized patients with cirrhosis were at risk of mortality, especially those developing ACLF. The CLIF-SOFA, CLIF-OF, CLIF-C, and ALCF grading systems were significantly associated with mortality among patients with ACLF but provided only modest means to discriminate mortality in our ACLF cohort. Finally, the predictive accuracies of the CLIF-SOFA, CLIF-OF, and CLIF-C grading systems were not superior to those of the MELD and MELD-Na scores among patients with ACLF according to the CLIF-C definition. Despite the limitations of using retrospective database, this study's results could have clinical implications as of potential assistance to physicians to target high-risk cirrhotic patients.

Acknowledgment

We thank Mr. Thomas Mc Manamon from the Office of Research and Development, Phramongkutklao College of Medicine, for English language editing.

References

- 1 Moreau R, Jalan R, Gines P *et al.* Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013; **144**: 1426, e9–37.
- 2 Sarin SK, Kedarisetty CK, Abbas Z *et al.* Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. *Hepatol. Int.* 2014; **8**: 453–71.

- 3 Blei A, Cordoba J, Practice Parameters Committee of the American College of Gastroenterology. Hepatic encephalopathy. *Am. J. Gastroenterol.* 2001; **96**: 1968–75.
- 4 Choudhury A, Jindal A, Maiwall R *et al.* Liver failure determines the outcome in patients of acute-on-chronic liver failure (ACLF): comparison of APASL ACLF research consortium (AARC) and CLIF-SOFA models. *Hepatol Int.* 2017; **11**: 461–71.
- 5 Cholongitas E, Papatheodoridis GV, Vangeli M *et al.* Systematic review: the model for end-stage liver disease—should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Aliment. Pharmacol. Ther.* 2005; **22**: 1079–89.
- 6 Wiesner R, Edwards E, Freeman R *et al.* Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003; **124**: 91–6.
- 7 Kim WR, Biggins SW, Kremers WK *et al.* Hyponatremia and mortality among patients on the liver-transplant waiting list. *N. Engl. J. Med.* 2008; **359**: 1018–26.
- 8 Zaccherini G, Weiss E, Moreau R. Acute-on-chronic liver failure: definitions, pathophysiology and principles of treatment. *JHEP Rep.* 2021; **3**: 100176.
- 9 Hernaez R, Kramer JR, Liu Y *et al.* Prevalence and short-term mortality of acute-on-chronic liver failure: a national cohort study from the USA. *J. Hepatol.* 2019; **70**: 639–47.
- 10 Jalan R, Gines P, Olson JC *et al.* Acute-on chronic liver failure. *J. Hepatol.* 2012; **57**: 1336–48.
- 11 Song DS, Kim TY, Kim DJ *et al.* Validation of prognostic scores to predict short-term mortality in patients with acute-on-chronic liver failure. *J. Gastroenterol. Hepatol.* 2018; **33**: 900–9.
- 12 Vincent J-L, Moreno R, Takala J *et al.* The SOFA (Sepsis-Related Organ Failure Assessment) Score to Describe Organ Dysfunction/Failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996; **22**: 707–10.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. CLIF-SOFA score.