Original Article

Clinical Outcome and Prognosis of Acute-on-Chronic Liver Failure: Experience from a Tertiary Care Center

Sirimongkolkasem J, MD[1,2], Teerasarntipan T, MD[1,2], Wongkarnjana A, MD[1,2], Thanapirom K, MD[1,2], Chaiteerakij R, MD, PhD[1,2], Phathong C, MA[1], Komolmit P, MD[1,2], Tangkijvanich P, MD, PhD[3], Treeprasertsuk S, MD, PhD[1,2]

[1] Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[2] Thai Red Cross Society, Bangkok, Thailand
[3] Liver Research Unit, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Objective: The Acute on Chronic Liver failure (ACLF) diagnostic criteria and prognostic score have been well established and the major cause for cirrhosis is chronic alcoholic liver disease (CANONIC study). However, this criteria has not yet been studied in Asia, where chronic hepatitis infection is more prevalent. We aimed to determine the outcome of Thai patients with ACLF and validate the CLIF-C organ failure (CLIF-C OF) score for ACLF diagnosis and CLIF-ACLF score for predicting prognosis.

Materials and Methods: We prospectively enrolled cirrhotic patients hospitalized with acute decompensation (AD). Primary end point was 3-month mortality. Factors associated with mortality were determined using logistic regression analysis.

Results: We enrolled 95 cirrhotic patients with mean age of 56 years. The most common etiology of cirrhosis was chronic viral hepatitis (48.5%) and alcoholism (44.2%). Forty patients (42%) were diagnosed with ACLF. The 3-month mortality rate was well correlated with the 3 ACLF subclasses, i.e. 45.5%, 53.6% and 80%, respectively. From the multivariate analysis, CLIF-ACLF score was the only independent predictor for the 3-month mortality in the ACLF group (adjusted OR 1.114, $p = 0.008$). Additionally, CLIF-ACLF score had the AUROC of 0.78 which was significantly higher than the other 4 scores studied ($p<0.05$).

Conclusion: ACLF is a distinct condition associated with high mortality and organ failures. CLIF-C organ failure (CLIF-C OFs) and CLIF-ACLF scores can be used to diagnose, classify and prognose ACLF in the Thai population.

Keywords: Acute-on-chronic liver failure, Outcome, Prognosis

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Acute decompensation (i.e., ascites, encephalopathy, gastrointestinal hemorrhage, bacterial infection) in cirrhotic patients often results in hospitalization[1-4]. These patients can be classified into two groups: the first one comprised of patients with organ failure(s) and the other group is those without organ failures. The group with organ failure(s) is considered to have acute-on-chronic liver failure (ACLF) and is characterized to have an extremely poor short-term survival rate. Mortality at 28 days and 90 days in ACLF patients are 33.9% and 51.2%, respectively[5]. The concept of ACLF has been well established in chronic liver failure (CLIF) Acute -on-chronic Liver Failure in Cirrhosis (CANONIC)[5] study which was a multicenter, European, prospective observational study conducted in cirrhotic patients admitted for acute decompensation[5].

Correspondence to:

Treeprasertsuk S.

Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Rama 4 Road, Pathumwan, Bangkok 10330, Thailand.

Phone: +66-2-2564265, Fax: +66-2-2527839

E-mail: battan5410@gmail.com

ACLF has a prevalence of approximately 12 to 30% in cirrhotic patients admitted with acute decompensation[5,6]. It occurs more frequently in alcoholic and hepatitis B associated liver disease patients. The most frequent acute insults resulting in the development of ACLF are bacterial infection, active alcoholism, or acute reactivation of hepatitis B[5].

A number of scoring systems were developed to predict outcomes for patients with ACLF. The Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) scoring system and simplified Chronic Liver Failure-Consortium Organ Failure score (CLIF-C OFs) were developed to diagnose ACLF using database from the CANONIC study. Subsequently, a specific prognostic score for ACLF (Chronic Liver Failure-Consortium Acute on Chronic Liver Failure score [CLIF-C ACLFs]) was developed by combining CLIF-C OFs with two independent mortality predictors (age and white blood cell count) and proved to have superior predictive accuracy than Model for End-stage Liver (MELD), MELD-sodium, and Child-Turcotte-Pugh (CTP) scores[5,7].

Both CLIF-C OFs and CLIF-C ACLF scores were well established in the European population with chronic alcoholic liver disease, which is the major cause for chronic

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liver diseases[5,7]. Performance of these scores in the Asian population, of which chronic hepatitis B (CHB) and chronic hepatitis C (CHC) infection are more prevalent, has not yet been studied[8,9].

The purpose of our study is to determine the epidemiology, outcome and prognosis of cirrhotic Thai patients with acute liver decompensation. Moreover, we aimed to determine whether CLIF-C OF score can be used to diagnose and classify ACLF or not. Lastly, we evaluated CLIF-ACLF score against the 5 conventional prognostic scores (MELD, MELD-Na, CTP score and CLIF-C OFs) to identify the best prognostic score to determine the short-term mortality among Thai ACLF patients from a tertiary care center.

Materials and Methods

Study design and data collection

We prospectively enrolled cirrhotic patients hospitalized with acute liver decompensation at the King Chulalongkorn Memorial Hospital between February 2012 and October 2016. Demographic data, etiology of liver cirrhosis, and the precipitating factors resulting in acute decompensation were collected from both out-patient and in-patient medical records. Clinical and laboratory data were collected within 24 hours after admission. These baseline data were used to diagnose ACLF, classified patients into ACLF subclasses and calculated other prognostic scores including MELD, MELD-Na and CTP scores. The duration of hospital stay, mortality rate at 28 days and 90 days were collected through the patients' medical records or by directly interviewing the patients or their relatives.

Patients

The diagnosis of cirrhosis was made based on a composite of clinical signs and findings provided by laboratory testing results, endoscopy, and radiological imagings. Acute decompensation was defined as having acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infection, hyperbilirubinemia, acute kidney injury, coagulopathy, hypoxemia, hemodynamic instability, or a combination of these things.

Diagnostic criteria of ACLF and its prognostic scores

ACLF was a syndrome that occurs in cirrhotic patients and is characterized by organ failure(s) and high mortality[10]. The diagnosis of organ failure(s) was made by using simplified organ function scoring system (CLIF-C OFs)[7]. Organ or system failures were defined as having any of the following conditions: 1) serum bilirubin ≥12 mg/dL for liver failure; 2) serum creatinine ≥2 mg/dL or requiring renal replacement therapy or kidney failure; 3) grade III to IV hepatic encephalopathy for brain failure; 4) INR ≥2.5 for coagulation failure; 5) vasoconstrictor requirements in maintaining normal arterial pressure for circulatory failure; and 6) PaO_2/FiO_2 ≤200 or SpO_2/FiO_2 ≤214 for lung failure. Patients with no organ failure, non-renal organ failure without cerebral and/or renal dysfunction (serum creatinine ≤1.5 mg/dL) or single cerebral failure with serum creatinine ≤1.5 mg/dL were considered to be free of ACLF.

Patients diagnosed with ACLF were further classified into 3 groups based on the number and severity of the organ failures: 1) ACLF-1 was defined as patients with (a) single kidney failure, (b) non-renal organ failure with mild to moderate hepatic encephalopathy and/or renal dysfunction (serum creatinine ≥1.5 mg/dL), or (c) single cerebral failure with serum creatinine ≥1.5 mg/dL; 2) ACLF-2 was defined as patients with 2 organ failures; and 3) ACLF-3 was defined as patients with more than 2 organ failures.

A combination of CLIF-C OFs with age and white blood cell count was used to calculate for the prognostic score for ACLF (CLIF-C ACLF) as per EASL-CLIF consortium.

Statistical analyses

Data are presented as mean and standard deviation (SD) for continuous data or frequency and percentage for categorical data. Student t-test and Chi-square or one-way ANOVA were used to compare the baseline characteristics between the 2 groups. Logistic regression analysis was performed to identify factors significantly associated with mortality. Area under the receiver operating characteristic (AUROC) curve was generated to assess the predictive performance of each mortality predictive score. The precision comparison between predictive scores was performed by using DeLong test. The *p*-value of <0.05 indicates statistical significance.

Results

Baseline characteristics

We screened and enrolled 95 cirrhotic patients, who had acute decompensation at first presentation and were admitted at our hospital. The mean age was 56 years and most patients (65.3%) were males. CHB and CHC infections (n = 46, 48.5%) followed by chronic alcoholic liver disease (n = 42, 44.2%) were the most common etiology for cirrhosis in this cohort. The most common potential precipitating events for ACLF were bacterial infection (n = 40, 42.1%), followed by GI hemorrhage (n = 27, 28.4%) and active alcohol consumption (n = 4, 4.2%). The most common organ and system failures were brain (n = 28, 29.5%), followed by kidney (n = 23, 24.2%), liver (n = 19, 20%), circulatory (n = 19, 17.9%), lung (n = 11, 11.6%), and coagulation (n = 6, 6.3%). Fifteen patients (15.8%) and thirteen (13.7%) patients had renal and cerebral dysfunction, respectively. From the univariate analysis, CTP, MELD, MELD-Na, CLIF-C-OF scores and the presence of kidney or hemodynamic failures were associated with a 90-day mortality (Table 1).

Clinical characteristics of patients with ACLF upon admission

Forty patients (42.1%) were diagnosed with ACLF

Table 1. Characteristics and mortality of cirrhotic patients with and without ACLF

	No ACLF (n = 55)	ACLF all grades (n = 40)	*p*-value	ACLF grade I (n = 11)	ACLF grade II (n = 19)	ACLF grade III (n = 10)	*p*-value
Age (years), mean (SD)	56 (13)	56 (15)	0.92	62 (16)	54 (13)	56 (17)	0.53
Male gender, n (%)	37 (67.3)	25 (62.5)	0.63	5 (45.5)	14 (73.7)	6 (60)	0.44
MAP (mmHg), mean (SD)	92 (16)	77 (20)	<0.001	87 (15)	76 (21)	70 (19)	<0.001
Etiology, n (%)							
Alcohol	13 (23.6)	11 (27.5)	0.67	2 (18.2)	6 (31.6)	3 (30)	0.83
HBV	9 (16.4)	4 (10)	0.37	1 (9.1)	3 (15.8)	0	0.53
HCV	8 (14.5)	7 (17.5)	0.70	2 (18.2)	3 (15.8)	2 (20)	0.97
Alcohol + HCV	8 (14.5)	4 (10)	0.51	3 (27.3)	1 (5.3)	0	0.19
Alcohol + HBV	2 (3.6)	4 (10)	0.24	1 (9.1)	2 (10.5)	1 (10)	0.66
NAFLD	4 (7.3)	2 (5)	1.00	0	0	2 (20)	0.15
Cryptogenic	8 (14.5)	4 (10)	0.51	1 (9.1)	1 (5.3)	2 (20)	0.63
Others	3 (5.5)	4 (10)	0.45	1 (9.1)	3 (15.8)	0	0.38
Potential precipitating events of ACLF, n (%)							
Alcohol	1 (1.8)	3 (7.5)	0.31	2 (18.2)	1 (5.3)	0 (0)	0.09
Bacterial infection	21 (38.2)	19 (47.5)	0.36	3 (27.3)	10 (52.6)	6 (60)	0.32
GI hemorrhage	17 (30.9)	10 (25)	0.53	3 (27.3)	5 (26.3)	2 (20)	0.91
Unknown	8 (14.5)	7 (17.5)	0.70	3 (27.3)	3 (15.8)	1 (10)	0.70
Others	8 (14.5)	1 (2.5)	0.07	0	0	1 (10)	0.19
Organ/system failure, n (%)							
Liver	2 (3.6)	17 (42.5)	<0.001	3 (27.3)	7 (36.8)	7 (70)	<0.001
Renal	0	23 (57.5)	<0.001	7 (63.6)	8 (42.1)	8 (80)	<0.001
Cerebral	10 (18.2)	18 (45)	0.005	0	11 (57.9)	7 (70)	<0.001
Coagulation	1 (1.8)	5 (12.5)	0.08	0	0	5 (50)	<0.001
Hemodynamic	3 (5.5)	14 (35)	<0.001	0	9 (47.4)	5 (50)	<0.001
Lung	2 (3.6)	9 (22.5)	0.005	1 (9.1)	3 (15.8)	5 (50)	<0.001
Kidney dysfunction	0	15 (37.5)	<0.001	3 (27.3)	6 (31.6)	6 (60)	<0.001
Cerebral dysfunction	5 (9.1)	8 (20)	0.13	6 (54.5)	2 (10.5)	0 (0)	<0.001
Baseline lab, mean (SD)							
Hemoglobin (g/dl)	10 (3)	9 (2)	0.09	10 (2)	9 (2)	9 (2)	0.15
Hematocrit (%)	30 (6)	28 (6)	0.046	31 (4)	27 (6)	26 (7)	0.06
Total bilirubin (mg/dL)	5 (4)	14 (14)	<0.001	7 (9)	13 (12)	23 (16)	<0.001
INR	2 (0.5)	2 (2)	0.08	1 (0.4)	2 (0.4)	3 (4)	0.001
AST (U/L)	152 (353)	210 (467)	0.49	63 (50)	185 (248)	420 (862)	0.19
ALT (U/L)	81 (171)	77 (87)	0.74	26 (13)	86 (102)	91 (92)	0.66
Creatinine (mg/dL)	0.9 (0.3)	3 (2)	<0.001	3 (2)	2 (1.7)	3 (2)	<0.001
Sodium (mmol/L)	134 (6)	132 (7)	0.067	130 (8)	134 (7)	129 (6)	0.04
Platelets ($x10^9$/L)	121 (80)	121 (96)	0.99	129 (58)	133 (126)	90 (55)	0.63
Hepatic encephalopathy, n (%)			0.018				<0.001
Grade 0-II	44 (80)	23 (57.5)		11 (100)	8 (42.1)	4 (40)	
Grade III-IV	11 (20)	17 (42.5)		0	11 (57.9)	6 (60)	
PaO_2/FiO_2			1.00				0.46
<200	0	1 (20)		0	0	1 (33.3)	
200-300	2 (100)	4 (80)		2 (100)	2 (100)	2 (66.7)	
Urine NGAL1, median (range)	28.2 (8.6 to 9,453)	106 (0.6 to 8,141)	<0.001	52.5 (22.2 to 6,993)	58.5 (0.6 to 1,762.2)	296.7 (39 to 8,141)	0.08
Urine NGAL2, median (range)	33.6 (3.8 to 9,990)	75.6 (3.8 to 8,141)	0.002	62.4 (24.3 to 6,993)	59.7 (3.8 to 1,281.6)	244.1 (39 to 8,141)	0.09
White blood count ($x10^9$/L), mean (SD)	9.3 (6.2)	9.9 (6.6)	0.63	9.5 (8.0)	10.7 (7.2)	8.8 (3.4)	0.83
Child-Pugh score, mean (SD)	8.4 (1.5)	11 (2)	<0.001	9 (2)	11 (2)	12 (1)	<0.001
MELD score, mean (SD)	16.4 (5.5)	26 (8)	<0.001	22 (3)	26 (6)	32 (11)	<0.001
MELD-sodium score, mean (SD)	18.8 (6.8)	29 (7)	<0.001	25 (4)	28 (6)	33 (9)	<0.001
LOS (days), median (range)	5 (0 to 128)	8 (1 to 54)	0.08	8 (2 to 50)	9.5 (2 to 54)	6 (1 to 52)	0.95
Mortality, n (%)							
1 month	7 (12.7)	17 (42.5)	0.001	2 (18.2)	8 (42.1)	7 (70)	<0.001
3 month	12 (24)	23 (57.5)	0.001	5 (45.5)	10 (52.6)	8 (80)	0.004
6 month	16 (34)	24 (64.9)	0.005	5 (50)	10 (55.6)	9 (100)	0.003

ACLF = acute on chronic liver failure, AST = aspartate aminotransferase, ALT = alanine aminotransferase, FiO2 = fraction of inspired oxygen, GI = gastrointestinal, INR = international normalized ratio, HBV = hepatitis B virus, HCV = hepatitis C virus, LOS = length of stay, MAP = mean arterial pressure, MELD = Model For End-stage Liver Disease, NAFLD = non-alcoholic fatty liver disease, NGAL = neutrophil gelatinase-associated lipocalin, PaO_2 = partial pressure of arterial oxygen

which was further classified based on the organ failures (Table 1). Eleven patients (27.5%) were classified with ACLF-1. Nineteen patients (47.5%) were classified with ACLF-2. Ten patients (25%) were classified with ACLF-3. The mean age of ACLF patients was 56 years which was comparable to the non ACLF patients. Most ACLF patients were males.

The mean arterial pressure of the ACLF group was significantly lower than the non-ACLF group (77 vs. 92 mmHg, $p<0.001$). The most common etiologies for cirrhosis in the ACLF group were CHB or CHC (47.5%) and alcohol (47.5%). Primary acute insults of ACLF were bacterial infection (47.5%) and GI hemorrhage (25%).

From the univariate analysis, hematocrit, total bilirubin, serum creatinine, hepatic encephalopathy, urine NGAL, CTP, MELD and MELD-Na were found to be associated with the presence of ACLF upon admission (Table 2). Any organ failure, except for coagulation failure, was also correlated with the presence of ACLF. In contrast, ACLF patients showed no significant difference in white blood counts (WBC) (9.9 ± 6.6 vs. 9.3 ± 6.2, $p = 0.63$). The median duration of hospital stay between ACLF and non-ACLF groups were comparable (5 days vs. 8 days, $p<0.08$).

Mortality of ACLF

The overall mortality in our cohort at 28 days and 90 days were 25.3% and 36.8%, respectively. The death rate at 28 days (12.7% vs. 42.5%, $p = 0.001$) and 90 days (24% vs. 57.5%, $p = 0.001$) were significantly higher in the ACLF group than the non-ACLF group. Association between mortality rates and the presence and severity of organ failures was observed. The patients with higher ACLF subclass had higher death rates at 28 days and 90 days (Table 1 and Figure 1). The death rates at 28 days and 90 days for ACLF-1 were 18.2% and 45.5%, respectively. The death rates at 28 days and 90 days for ACLF-2 were 42.1% and 52.6%, respectively. The death rates at 28 days and 90 days for ACLF-3 were 70% and 80%, respectively.

From the univariate analysis, age and CLIF-ACLF score were the only 2 predictors for short-term mortality.

Table 2. Univariate and multivariate analysis of 90-day mortality in hospitalized cirrhotic patients with acute decompensation

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age, years	1.02 (0.99 to 1.05)	0.19		
Sex, males	0.84 (0.45 to 2.66)	0.84	1.18 (0.43 to 3.24)	0.74
Mean arterial pressure	0.98 (0.96 to 1.00)	0.10		
Organ/system failures				
Liver	2.04 (0.73 to 5.69)	0.17		
Kidney	3.41 (1.27 to 9.11)	0.015	1.97 (0.47 to 8.24)	0.35
Brain	1.95 (0.79 to 4.84)	0.15		
Coagulation	3.42 (0.59 to 19.76)	0.17		
Hemodynamic	5.22 (1.65 to 16.55)	0.005	2.11 (0.46 to 9.68)	0.34
Lung	3.19 (0.86 to 11.84)	0.08		
Kidney dysfunction	2.83 (0.91 to 8.81)	0.07		
Cerebral dysfunction	1.14 (0.33 to 3.93)	0.83		
Baseline lab				
Hemoglobin (g/dL)	0.86 (0.71 to 1.04)	0.12		
Hematocrit (%)	0.95 (0.88 to 1.02)	0.14		
Total bilirubin (mg/dL)	1.03 (0.99 to 1.08)	0.11		
INR	1.27 (0.79 to 2.04)	0.33		
AST (U/L)	1.00 (1.00 to 1.00)	0.49		
ALT (U/L)	1.00 (1.00 to 1.00)	0.61		
Creatinine (mg/dl)	1.18 (0.90 to 1.55)	0.23		
Sodium (mmol/L)	0.95 (0.89 to 1.02)	0.13		
Platelets ($x10^9$/L)	1.00 (1.00 to 1.00)	0.58		
WBC count	1.00 (1.00 to 1.00)	0.97		
Hepatic encephalopathy	1.73 (0.69 to 4.32)	0.24		
Urine NGAL1	1.00 (1.00 to 1.00)	0.75		
Urine NGAL2	1.00 (1.00 to 1.00)	0.72		
Prognostic score				
Child-Pugh score	1.24 (1.01 to 1.53)	0.036	0.93 (0.62 to 1.40)	0.74
MELD score	1.07 (1.01 to 1.13)	0.023	0.90 (0.73 to 1.11)	0.32
MELD-Na score	1.07 (1.02 to 1.14)	0.011	1.11 (0.92 to 1.34)	0.27
CLIF-OF score	1.46 (1.17 to 1.81)	0.001	1.36 (0.87 to 2.13)	0.18
Length of stay	1.01 (0.99 to 1.04)	0.43		

AST = aspartate aminotransferase, ALT = alanine aminotransferase, CLIF-OF score = Chronic Liver Failure-Organ Failure score, INR = international normalized ratio, MELD = Model For End-stage Liver Disease, WBC = white blood cells

WBC and urine NGALs were interestingly not correlated with 3-month mortality. The etiology for cirrhosis (viral vs. non-viral) was not associated with the 3-month survival. From the multivariate analysis, after adjusted for sex, the CLIF-ACLF score was the only predictor for the 90-day mortality in ACLF patients (adjusted OR 1.114, 95% CI 1.035 to 1.264, $p = 0.008$) (Table 3).

CLIF-ACLF score had the highest performance with AUROC of 0.78, (95% CI 0.623 to 0.896, $p<0.05$) in predicting the 3-month mortality when compared to the other 4 predictive scores. AUROCs for CLF-C OF, CTP, MELD, and MELD-Na scores were 0.607 (95% CI 0.441 to 0.758), 0.513 (95% CI 0.350 to 0.674), 0.540 (95% CI 0.375 to 0.698), and 0.542 (0.377 to 0.700), respectively (Figure 3).

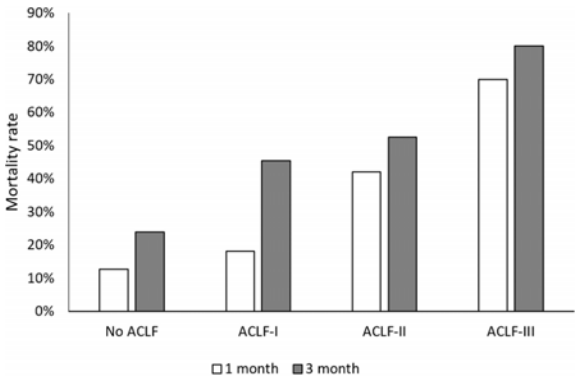


Figure 1. 28-day and 90-day mortality rates based on the acute-on-chronic liver failure (ACLF) subclasses.

Discussion

The diagnosis and prognostic criteria for ACLF

Table 3. Univariate and multivariate analysis of 90-day mortality in ACLF patients

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age, years	1.09 (1.02 to 1.16)	0.009		
Sex, males	0.85 (0.23 to 3.11)	0.80	0.94 (0.21to 4.14)	0.93
Length of stay	1.01 (0.96 to 1.06)	0.71		
Mean arterial pressure	0.99 (0.96 to 1.02)	0.48		
Organ/system failures				
Liver	1.10 (0.31 to 3.91)	0.88		
Kidney	1.38 (0.39 to 4.92)	0.62		
Brain	1.31 (0.37 to 4.64)	0.68		
Coagulation	3.37 (0.34 to 33.26)	0.30		
Hemodynamic	4.28 (0.96 to 19.01)	0.06		
Lung	1.65 (0.35 to 7.81)	0.53		
Kidney dysfunction	1.18 (0.32 to 4.33)	0.84		
Cerebral dysfunction	0.68 (0.14 to 3.24)	0.63		
Baseline lab				
Hemoglobin (g/dL)	0.94 (0.70 to 1.26)	0.68		
Hematocrit (%)	0.98 (0.88 to 1.01)	0.76		
Total bilirubin (mg/dL)	1.00 (0.95 to 1.05)	0.99		
INR	1.19 (0.71 to 1.98)	0.51		
AST (U/L)	1.00 (1.00 to 1.00)	0.43		
ALT (U/L)	1.00 (1.00 to 1.01)	0.36		
Creatinine (mg/dl)	0.93 (0.68 to 1.28)	0.66		
Sodium (mmol/L)	0.95 (0.87 to 1.04)	0.31		
Platelet ($x10^9$/L)	1.00 (1.00 to 1.00)	0.24		
WBC count	1.00 (1.00 to 1.00)	0.86		
Hepatic encephalopathy	1.01 (0.31 to 3.91)	0.88		
Urine NGAL1	1.00 (1.00 to 1.00)	0.78		
Urine NGAL2	1.00 (1.00 to 1.00)	0.68		
Prognostic score				
Child-Pugh score	1.00 (0.76 to 1.33)	0.98		
MELD score	1.01 (0.93 to 1.09)	0.86		
MELD-Na score	1.02 (0.93 to 1.12)	0.69		
CLIF-OF score	1.25 (0.88 to 1.76)	0.21		
CLIF-ACLF score	1.14 (1.04 to 1.26)	0.008	1.14 (1.04 to 1.26)	0.008

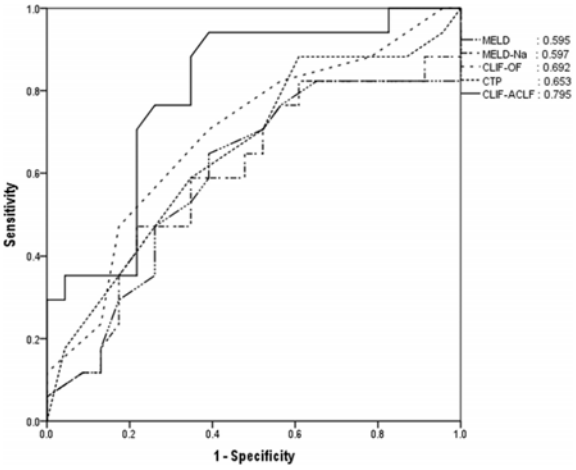
AST = aspartate aminotransferase, ALT = alanine aminotransferase, CLIF-OF score = Chronic Liver Failure-Organ Failure score, INR = international normalized ratio, MELD = Model For End-stage Liver Disease, WBC = white blood cells

has been well studied in the European population, of whom the major cause of cirrhosis are alcoholism and CHC[5,7,11]. Thus, its use may not be applicable for the Thai population due to clinical differences of cirrhosis. In the present study, viral hepatitis was relatively more prevalent than alcoholism when compared to the CANONIC study[5] (48.4% vs. 29.1% and 44.2% vs. 61.5%, respectively).

Results of this study proved that CLIF-C OF score could effectively diagnose ACLF in cirrhotic patients hospitalized with acute decompensation and subclass of ACLF. The mortality rate of the patients with ACLF was significantly higher than those without ACLF and this increased in patients with severe ACLF subclass. The short-term mortality rate for each ACLF subclass was close to those reported in the CANONIC study[5]. However, we found that the 28-day and 90-day death rates were higher in the non-ACLF group when compared to the previous study (12.7% vs. 4.7% and 24% vs. 14%, respectively)[5]. This could be explained by the higher proportion of patients with bacterial infection that could result in sepsis, contributing to higher rates of overall mortality in the non-ACLF group.

The WBC level, which represents the systemic inflammation level, was assumed to play a pivotal role in the pathogenesis of ACLF[5,12]. Higher level of WBC was found to be associated with poorer survival rate[5]. However, the level of the WBC was not correlated with the patients' mortality by the univariate analysis in the present study. The reason may be due to higher baseline MELD score or more severe status of the liver cirrhosis in our patients compared to the patients from the CANONIC study (21 vs. 19). The immune regulatory system in our patients might be more suppressed than those in the previous study, which could result in lower number of WBC count. Moreover, a higher proportion of our patients have bacterial infection which can contribute to the development of sepsis. In severe sepsis, the number of WBC can either fall below $4x10^9$/L, or above $12x10^9$/L[13,14]. The ratio of neutrophils to lymphocytes or the level of specific inflammatory cytokines such as TNF-alpha and interleukin-6 may help decrease the variability of the result in future study.

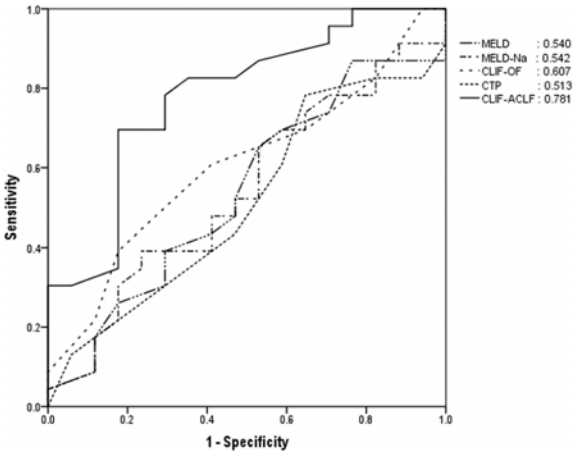
CLIF-ACLF score was developed to predict prognosis of patients with ACLF by combining WBC count and age to the CLIF-C OF score and has already been validated



	AUROC (95% CI)	*p*-value*
MELD	0.595 (0.428 to 0.747)	0.037
MELD-Na	0.597 (0.431 to 0.749)	0.050
CLIF-OF	0.692 (0.526 to 0.828)	0.155
CTP	0.653 (0.487 to 0.797)	0.081
CLIF-ACLF	0.795 (0.638 to 0.906)	Reference

MELD score = Model For End-stage Liver Disease score, MELD-Na score = Model For End-stage Liver Disease-Sodium score, CLIF-OF score = Chronic Liver Failure-Organ Failure score, CTP = Child-Pugh score-CLIF-ACLF score, Chronic Liver Failure-Consortium Acute on Chronic Liver Failure score

Figure 2. AUROC of CLIF-ACLF score for predicting 28-day mortality in comparison with other prognostic scores.



	ROC (95% CI)	*p*-value
MELD	0.540 (0.375 to 0.698)	0.010
MELD-Na	0.542 (0.377 to 0.700)	0.015
CLIF-OF	0.607 (0.441 to 0.758)	0.021
CTP	0.513 (0.350 to 0.674)	0.001
CLIF-ACLF	0.781 (0.623 to 0.896)	Reference

MELD score = Model For End-stage Liver Disease score, MELD-Na score = Model For End-stage Liver Disease-Sodium score, CLIF-OF score = Chronic Liver Failure-Organ Failure score, CTP = Child-Pugh score-CLIF-ACLF score, Chronic Liver Failure - Consortium Acute on Chronic Liver Failure score

Figure 3. AUROC of CLIF-ACLF score for predicting 90-day mortality in comparison with other prognostic scores.

in many studies[7,15]. In the present study, though the WBC count was not an independent predictor for mortality, the performance of CLIF-ACLF against other prognostic scores had excellent AUROC when compared to the previous study[7,15]. The results were consistent for 28-day, 90-day, and 180-day mortality rates.

This study has some limitations. First, the total number of patients included in the study was quite small, with only 40 patients who had fulfilled the ACLF diagnostic criteria. Although there were significant differences of mortality between each group, the result might not represent the whole studied population due to lack of data distribution. Second, this study was conducted in only one tertiary center. The study result might be unable to be generalized to Thai patients in other parts of the country with different medical facility levels. Therefore, the multi-centered study with larger number of ACLF patients are needed.

Conclusion

ACLF is a distinct condition which is associated with high mortality and organ failures. Our data provided unique clinical differences of cirrhotic patients presented with acute decompensation and proved that the CLIF-C-OF and CLIF-ACLF scores were excellent tools in diagnosing, classifying, and predicting short-term mortality among Thai patients with ACLF.

What is already known on this topic?

According to EASL definition, ACLF is defined as an acute deterioration of pre-existing liver cirrhosis and associated with high short-term mortality due to systemic organ failures. CLIF-C-OF and CLIF-C-ACLF scores were developed and proven effective for ACLF diagnosis, severity classification and short-term mortality prediction among European population. WBC count and age are independent predictors of mortality and are included in CLIF-C-ACLF score for prognosis prediction.

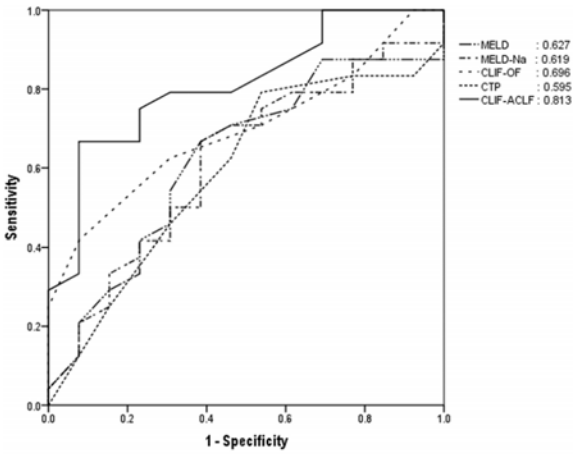
What this study adds?

Although the cause of cirrhosis among Thai patients are different from European patients, our study provided similar clinical outcome and prognosis of ACLF. We also confirmed the efficacy of both CLIF-C-OF and CLIF-C-ACLF scores. WBC count was not associated with worse

Table 4. Baseline characteristics of patients in the present study versus those from the CANONIC study

	Present study (n = 95)	CANONIC study (n = 1,343)
Age (years), mean (SD)	56 (14)	57 (12)
Male gender, n (%)	62 (65.3)	850 (63.3)
MAP (mmHg), mean (SD)	86 (19)	82 (13)
Etiology, n (%)		
Alcohol	24 (25.3)	659 (51.9)
HCV	15 (15.8)	248 (18.5)
Alcohol + HCV	12 (12.6)	122 (9.1)
Potential precipitating events of ACLF, n (%)		
Alcohol	4 (4.2)	216 (16)
Bacterial infection	40 (42.1)	324 (24)
GI hemorrhage	27 (28.4)	220 (16.4)
Others	24 (25.3)	59 (4.4)
Organ/system failure, n (%)		
Liver	19 (20)	207 (15.4)
Kidney	23 (24.2)	169 (12.6)
Brain	28 (29.5)	99 (7.4)
Coagulation	6 (6.3)	105 (7.8)
Lung	11 (11.6)	32 (2.4)
Kidney dysfunction	15 (15.8)	136 (10)
Cerebral dysfunction	13 (13.7)	362 (27)
Baseline lab, mean (SD)		
Hematocrit (%)	29 (6)	31 (6)
Total bilirubin (mg/dL)	8.4 (10)	6.6 (10.8)
INR	1.8 (1.4)	1.7 (0.6)
AST (U/L)	176 (403)	104 (182)
ALT (U/L)	76 (141)	57 (122)
Creatinine (mg/dL)	1.6 (1.5)	1.3 (1)
Platelet ($x10^9$/L)	121 (86)	108 (75)
MELD score, mean (SD)	21 (8)	18.8 (7.5)
Child-Pugh score, mean (SD)	9.4 (2.1)	9.7 (2.1)

AST = aspartate aminotransferase, ALT = alanine aminotransferase, HCV = hepatitis C virus, INR = international normalized ratio, MAP = mean arterial pressure, MELD = Model for End-stage Liver Disease



	ROC (95% CI)	*p*-value
MELD	0.627 (0.453 to 0.780)	0.056
MELD-Na	0.619 (0.445 to 0.773)	0.060
CLIF-OF	0.696 (0.523 to 0.836)	0.123
CTP	0.595 (0.421 to 0.752)	0.012
CLIF-ACLF	0.813 (0.650 to 0.922)	Reference

MELD score = Model For End-stage Liver Disease score, MELD-Na score = Model For End-stage Liver Disease-Sodium score, CLIF-OF score = Chronic Liver Failure-Organ Failure score, CTP = Child-Pugh score-CLIF-ACLF score, Chronic Liver Failure-Consortium Acute on Chronic Liver Failure score

Figure 4. AUROC of CLIF-ACLF score for predicting 180-day mortality in comparison with other prognostic scores.

prognosis in our population. Further study of other inflammatory markers and lactate in ACLF patients for prognosis prediction is warranted.

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Potential conflicts of interest

Part of the information had been submitted to the 26th APASL annual meeting, held on February 15 to 19, 2017 at Shanghai, China.

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