Original Article

CLIF-SOFA and Urine Neutrophil Gelatinase-Associated Lipocalin Score for the Diagnosis of Acute-on-Chronic Liver Failure and as a Prognostic Tool for Mortality Prediction

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Objective: To validate the chronic liver failure-sequential organ failure assessment [CLIF-SOFA] tool for the diagnosis of acute-on-chronic liver failure [ACLF] in hospitalized Thai patients with cirrhosis and to evaluate the clinical significance of urine neutrophil gelatinase-associated lipocalin [uNGAL] in combination with the CLIF-SOFA score to predict ACLF mortality.

Materials and Methods: Seventy-seven patients were enrolled. The authors generated new ACLF diagnostic criteria by combining the uNGAL level with the original renal failure criteria from the CLIF-SOFA score [CLIF/NGAL score]. The primary endpoint was the 30-day mortality rate [MR].

Results: ACLF patients, according to the original CLIF-SOFA score, had a 43.7% MR in comparison to the non-ACLF patients, who had a 13.3% MR. The calculated odds ratio [OR] was 3.28, with an area under the ROC [AUROC] of 0.750 (95% CI 0.62 to 0.88, p = 0.001). The CLIF/NGAL score demonstrated better prognostic prediction ability. The MR was 38.6%, with an OR of 4.03 (95% CI 1.29 to 12.61) and an AUROC of 0.772 (95% CI 0.65 to 0.90, p<0.001).

Conclusion: The CLIF-SOFA score is valid for ACLF diagnosis among Thai patients. Moreover, the authors new proposed criteria, the CLIF/NGAL score, demonstrated better potential than the original criteria for ACLF mortality prediction.

Keywords: Renal failure, NGAL, Acute-on-chronic liver failure, Cirrhosis, Mortality

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Acute-on-chronic liver failure [ACLF] is a new condition that presents in patients with underlying chronic liver disease. When accompanied by certain precipitating factor(s), the liver function rapidly declines, leading to organ(s) failure and to high short-term mortality. If the precipitating factor was treated early, the liver function might return to the status before the event. In contrast, a delay in treatment can cause permanent liver damage, progress to end stage liver failure, and death[1,2].

The most widely accepted criterion for ACLF diagnosis was proposed by the EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis [CANONIC] study[1]. The present study adapted the sequential organ failure assessment [SOFA] score for proper use in patients with cirrhosis. The new score was called the CLIF-SOFA score, and it included six organ systems with their own criteria for organ failure diagnoses. The kidney is the most important organ in the CLIF-SOFA score in terms of short-term death. Generally, the serum creatinine level is the standard marker for renal function assessment, however, some factors, such as nutritional status and liver disease, can cause false levels[3]. Importantly, because the interval from the onset of renal injury to the rise in serum creatinine is at least 24 hours, the use of this marker may limit its sensitivity for ACLF detection.

Urine neutrophil gelatinase-associated lipocalin [uNGAL] is a new biomarker for acute kidney injury

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[AKI] diagnosis. Many studies have found that uNGAL is useful for the detection of AKI, especially during the early stage after renal injury when the rising serum creatinine level is still undetectable[4]. Treeprasertsuk et al[5] studied the clinical usefulness of uNGAL in AKI-prone Thai patients with cirrhosis and found that the mean uNGAL level was significantly higher in patients who developed AKI than in non-AKI patients and non-survivors.

To date, the CLIF-SOFA score is the most reliable criterion for ACLF diagnosis because it has demonstrated the best ability to predict short-term mortality. However, some characteristics in the CANONIC study population differed from Asian populations, especially in terms of etiologies and precipitating factors. Shalimar et al[6] found that different types of acute hepatic insult influenced the mortality of ACLF patients, resulting in different outcomes. Therefore, a clinical evaluation of the CLIF-SOFA score in Thai people is needed. We conducted the first study investigating ACLF in Thailand and Southeast Asia with the aim of validating the CLIF-SOFA score for the diagnosis of ACLF in Thai patients with cirrhosis. We also evaluated the clinical significance of uNGAL in combination with the CLIF-SOFA score for the prediction of mortality in ACLF patients.

Materials and Methods

Study design and ethics

The present study was a prospective observational study performed in King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The study period was between December 10, 2014, and November 30, 2015, with 30 days of follow-up. The study was reviewed and approved by the Institutional Review Board (IRB. Number 462/2557) of the Faculty of Medicine, Chulalongkorn University, on December 4, 2014. All the participants, or their legal guardians, provided written consents prior to the study enrollment. All the authors have no conflict of interest.

Patients and data collection

The inclusion criteria were 1) in-patients with Thai nationality, 2) age 18 years or older, 3) have cirrhosis confirmed by pathological or imaging studies, and 4) presented with acute liver decompensation (defined by acute development of cirrhosis-related complications such as ascites, encephalopathy, gastrointestinal bleeding, and bacterial infection). The exclusion criteria were 1) concomitant malignancy, 2) pregnancy, 3) severe co-morbidities or chronic kidney disease, and 4) currently receiving an immunosuppressant.

A detailed history and physical examination to detect acute decompensation was recorded. The initial laboratory data was measured within 24 hours after admission. The uNGAL sample was collected within 48 hours after admission and was immediately centrifuged at 1,500 rpm for 10 minutes, then, the supernatant was frozen at -70°C for batch analysis. The uNGAL level was measured with a chemiluminescent microparticle assay using the ARCHITECT platform (Abbott Diagnostics Inc., Abbott Park, IL, USA).

Procedures

Clinical information and laboratory profiles including the uNGAL level were collected within 48 hours after admission by the first author. The participants were classified into two groups (acute decompensation with ACLF or without ACLF). For the ACLF diagnosis, we generated a novel ACLF diagnostic criteria by combining the uNGAL level with the original renal failure criteria from the CLIF-SOFA score. Because a limited number of studies had investigated uNGAL and cirrhosis, a standard cut-off level was unavailable. Therefore, the authors applied findings from Treeprasertsuk et al[5], who investigated AKI-prone cirrhotic patients in the authors' hospital. The optimal cut-off level of uNGAL for AKI detection was 56 ng/mL (sensitivity 77.1%, specificity 73.3%), and 72 ng/mL was the best cut-off level for mortality prediction (sensitivity 70.6%, specificity 79.2%). Therefore, we applied these two cut-off points in the present study. Based on several systematic reviews, a higher uNGAL level corresponded to a poorer prognosis and death[5,7]. Hence, participants who met the original renal failure criteria or had a uNGAL level above our prespecified cut-off were not only diagnosed with renal failure but also had the highest renal failure (three points) scores (Table 1). The diagnostic criteria for the other organ failures remained the same. The authors called this proposed criterion the "CLIF/NGAL (n) score" (n referred to the cut-off point). The authors used the CLIF-c OFs score web-based calculator (www.clifconsortium.com/aclf-calculator/) to calculate the CLIF-SOFA and CLIF/NGAL scores. The ACLF patients were later categorized into three severity grades. Single kidney failure or single non-kidney with an abnormal serum creatinine level were the criteria for ACLF grade 1. Participants who had two or at least three organ failures were classified as ACLF grades 2 and 3, respectively. Standard treatment

Table 1. CLIF/NGAL score

Organ	Criterion	Score	Organ failure
Liver (bilirubin, mg/dL)	<6	1	No
	6.0 to ≤12.0	2	No
	>12	3	Yes
Kidney (creatinine, mg/dL)	<2	1	No
	2.0 to <3.5	2	No
	≥3.5 or renal replacement Rx or use vasopressor* or uNGAL ≥ cut-off	3	Yes
Hepatic encephalopathy	No hepatic encephalopathy	1	No
	West-Haven grade 1-2	2	No
	West-Haven grade 3-4 or on mechanical ventilation†	3	Yes
Coagulation (INR)	<2.0	1	No
	2.0 to <2.5	2	No
	≥2.5	3	Yes
Hemodynamic (MAP, mmHg)	≥70	1	No
	<70	2	No
	Use vasopressor	3	Yes
Lung			
PaO_2/FiO_2 ratio	>300	1	No
	>200 and ≤300	2	No
	≤200 or mechanical ventilation‡	3	Yes
SpO_2/FiO_2 ratio	>357	1	No
	>214 and ≤357	2	No
	≤214 on mechanical ventilation‡	3	Yes

INR = international normalized ratio; MAP = mean arterial pressure; Rx = therapy; uNGAL = urine neutrophil gelatinase-associated lipocalin

* For the indication of hepatorenal syndrome, † Alteration of consciousness from hepatic encephalopathy, ‡ For the indication of respiratory failure

This table was modified from the CLIF-SOFA score in combination with our proposed uNGAL criteria

was given, and no author was involved in the hospital care. The treatment outcome was evaluated at the end of the study by searching the medical records or by a direct phone call.

Statistical analysis

All the data were documented in electronic case record form. The estimated study size was seventy-six based on a 34% mortality rate [MR] as reported by the CANONIC study[1] with an absolute acceptable error of 10%. The categorical data were compared using Fisher's exact test. Continuous variables were described as the means and standard deviations. An independent samples t-test was used for comparisons between groups with normal distributions, and the Mann-Whitney (Wilcoxon rank) test was used to compare groups with non-normal distributions. The primary outcome was the 1-month MR. The secondary outcomes were the odds ratio [OR] and the area under receiver operator characteristic [AUROC] curves, which were used to evaluate the accuracy of each diagnostic test. A subgroup analysis was performed in patients with an initial serum creatinine level less than 2 mg/dL. All the tests were 2-sided, and the adopted *p*-value for the significance level was smaller than 0.05. SPSS for Mac (version 22.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The statistical methods of this study were reviewed by a statistician from the Research Affairs of the Faculty of Medicine, Chulalongkorn University.

Results

One thousand one hundred ninety-six patients with cirrhosis were hospitalized during the present study period, of which 184 patients had acute decompensation and were eligible for inclusion. After 107 subjects were excluded, 77 patients were recruited for the present study (Figure 1). None of the subjects were lost to follow up or underwent liver transplantation. The mean age was 56±13 years, and most of the patients were male. No significant differences in age, gender, cirrhosis etiologies, and precipitating factors were observed between the ACLF and non-ACLF groups. The laboratory profiles between the two groups showed no significant differences, except for the mean serum creatinine and bilirubin levels and the Model for End-Stage Liver Disease [MELD] scores, which were higher in the ACLF patients (Table 2).

Regarding the overall causes of cirrhosis, alcohol consumption, hepatitis C virus [HCV] infection, and

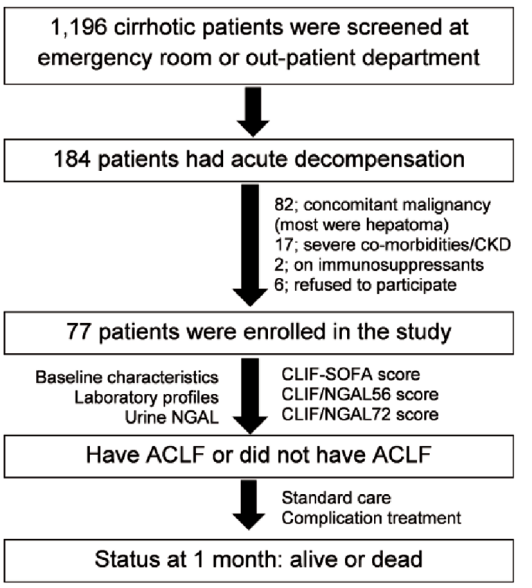

Figure 1. The study algorithm.

Table 2. Baseline characteristics of acute decompensated cirrhosis with or without ACLF

Characteristics	Overall (n = 77), mean ± SD	AD without ACLF (n = 45), mean ± SD	AD with ACLF (n = 32), mean ± SD	*p*-value
Age (years)	56±13	55.6±13.1	58.4±14.2	0.367
Male, n (%)	51 (66.2)	30 (66.7)	21 (65.6)	
Laboratory profiles				
Hb (g/dL)	9.4±2.2	9.7±2.2	9.3±2.0	0.380
Hct (%)	29±6	30±6	28±6	0.252
WBC count (103/µL)	9,494±6,412	9,239±6,697	10,478±7,015	0.441
Platelet count (109/L)	125±93	121±86	132±101	0.599
INR	1.8±1.5	1.6±0.5	2.1±2.2	0.128
Creatinine (mg/dL)	1.7±1.5	0.9±0.3	2.8±1.8	<0.001
Total bilirubin (mg/dL)	8.3±10.4	4.5±3.7	13.3±13.9	0.001
Direct bilirubin (mg/dL)	4.8±6.3	2.7±2.5	7.8±8.7	0.003
AST (U/L)	158±352	108±118	229±517	0.135
ALT (U/L)	71±110	70±120	74±93	0.876
ALP (g/dL)	148±102	145±93	151±113	0.814
Albumin (g/dL)	2.5±0.7	2.6±0.7	2.5±0.6	0.692
Total protein (g/dL)	6.9±1.3	6.7±1.4	7.0±1.3	0.500
MELD score	20.8±8.6	16.6±5.8	26.9±8.2	<0.001

AD = acute decompensation; ACLF = acute-on-chronic liver failure; Hb = hemoglobin; Hct = hematocrit'; WBC = white blood cell; INR = international normalized ratio; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; MELD = Model for End-Stage Liver Disease

Table 3. Effects from causes and insults on the 1-month mortality

Factors	Number of all cases, n (%)	Number of ACLF cases, n (%)	*p*-value	Odd ratio for mortality	95% CI
Etiologies					
Alcohol	21 (27.7)	9 (28.1)	0.544	1.02	0.43 to 2.43
HBV infection	10 (13.0)	4 (12.5)	0.598	0.54	0.09 to 3.08
HCV infection	11 (14.3)	5 (15.6)	0.513	0.90	0.28 to 2.85
NAFLD	5 (6.5)	1 (3.1)	0.303	2.39	1.58 to 3.61
Other cause	15 (19.5)	6 (18.8)	0.565	1.18	0.47 to 2.96
Alcohol/HBV	4 (5.2)	3 (9.4)	0.192	1.61	0.65 to 4.00
Alcohol/HCV	11 (14.3)	4 (12.5)	0.487	0.54	0.09 to 3.08
Precipitating factors					
GI hemorrhage	25 (32.5)	8 (25.0)	0.176	0.82	0.30 to 2.21
Alcohol	2 (2.6)	1 (3.1)	0.662	-	-
Bacterial infection	31 (40.3)	16 (50.0)	0.109	1.33	0.60 to 2.97
Drug-induced	2 (2.6)	1 (3.1)	0.662	2.39	1.58 to 3.61
HE	6 (7.8)	3 (9.4)	0.489	0.74	0.14 to 3.87
Unidentified	7 (9.1)	3 (9.4)	0.621	0.74	0.14 to 3.87

ACLF = acute-on-chronic liver failure; CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; NAFLD = non-alcoholic fatty liver disease; GI = gastrointestinal; HE = hepatic encephalopathy

mixed alcohol consumption with hepatitis B virus [HBV] infection had risks of mortality, but these variables had 95% confidence intervals [CIs] that crossed 1. For patients with ACLF, only NAFLD increased the risk of death, with a 95% CI greater than 1, whereas alcohol consumption and mixed alcohol consumption with HBV infection were at risk but had 95% CIs that crossed 1. Regarding the liver injury factors, every alcohol-induced liver injury patient survived. Bacterial infection and drug-induced liver injury increased the risk of death, but only drug-induced liver damage had a 95% CI greater than 1 (Table 3).

To validate the CLIF-SOFA score in Thai patients with cirrhosis, we assessed the MR of the 45 cases (58.4%) that did not meet the ACLF diagnostic criteria (13.33%). Thirty-two patients (41.6%) had ACLF and were categorized into three severity grades. All the criteria reflected the higher ACLF grading, which was correlated with higher mortality (Figure 2).

Forty-three and 28 patients had uNGAL levels above the cut-off levels of 56 ng/dL and 72 ng/dL, respectively. The MRs were 42.4% for the uNGAL56 group and 39.3% for the uNGAL72 group. Using the CLIF-SOFA score, 32 patients had ACLF, and 45 patients did not have ACLF; the corresponding MRs were 43.7% and 13.3%, respectively. Regarding the CLIF/NGAL56 score, 44 patients had ACLF, of which 17 patients (38.6%) died at follow-up. The 33 patients who did not meet the CLIF/NGAL56 criteria had 9.09%

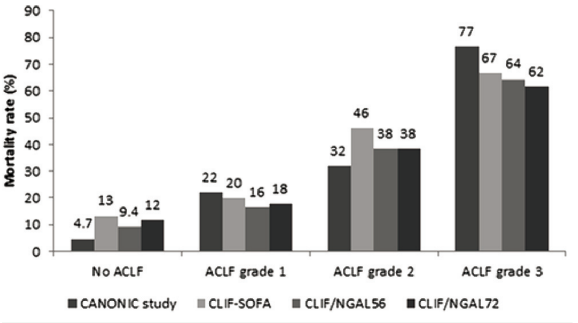

Figure 2. Mortality rate in each ACLF grade according to different criteria.

MR. Using the CLIF/NGAL72 criteria, 40 patients had ACLF, of which 15 patients (37.50%) died. In contrast, five of the 37 patients who did not have ACLF (13.5%) did not survive. The odd ratios between each diagnostic criterion are described in Table 4. The CLIF/NGAL56 score appeared to be the best predictor of mortality. As a screening tool, the CLIF/NGAL56 score had the best sensitivity (85.0%) and had 50.9% specificity, followed by the CLIF/NGAL72 score, the CLIF-SOFA score and the NGAL criteria. The CLIF/NGAL and CLIF-SOFA scores were calculated to determine the ACLF severity. The CLIF/NGAL56 score had the best accuracy for mortality prediction, with an AUROC of 0.772 (95% CI 0.65 to 0.90, $p<0.001$), a sensitivity of 75.0%, and a specificity of 71.9% at a cut-off score of 9.5. The AUROCs were 0.764, 0.750, and 0.656 for the CLIF/NGAL72, CLIF-SOFA, and MELD scores, respectively (Figure 3a, Table 5).

Finally, we analyzed the participants who had initial serum creatinine levels below 2 mg/dL (non-AKI subgroup). Fifty-five patients (71.43%) who did not have AKI were included in the subgroup analysis. The sensitivity of the ACLF diagnosis from each criterion in the subgroup analysis showed the same trend as the overall analysis. The CLIF/NGAL56 score remained the best prognostic predictor in the non-AKI subgroup patients (Figure 3b, Table 4, 5).

Discussion

Several studies from different continents have validated the use of the CLIF-SOFA score in acute decompensated cirrhosis patients, and they found that this score predicts short-term mortality more accurately

Table 4. Risk of death between ACLF and non-ACLF patients evaluated by different diagnostic scores

Criterion	OR	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall analysis						
NGAL56	3.11	1.34 to 7.23	70.0	66.7	42.4	86.4
NGAL72	2.14	1.01 to 4.52	55.0	70.2	39.3	81.6
CLIF-SOFA	3.28	1.41 to 7.62	70.0	68.4	43.8	86.7
CLIF/NGAL56	4.03	1.29 to 12.61	85.0	50.9	37.8	90.6
CLIF/NGAL72	2.63	1.06 to 6.53	75.0	54.4	36.6	86.1
Subgroup analysis in AKI-patients						
NGAL56	3.32	1.11 to 9.92	63.6	72.7	36.8	88.9
NGAL72	1.67	0.58 to 4.87	36.4	77.3	28.6	82.9
CLIF-SOFA	3.75	1.42 to 9.88	45.5	88.6	50.0	86.7
CLIF/NGAL56	3.71	1.10 to 12.49	72.7	65.9	34.8	90.6
CLIF/NGAL72	2.27	0.78 to 6.49	54.5	70.5	31.6	86.1

ACLF = acute-on-chronic liver failure; AKI = acute kidney injury; OR = odd ratio; CI = confidence interval; Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value

Table 5. Prediction accuracy for the 1-month mortality rate among ACLF patients who were diagnosed by different diagnostic scores

Criterion	AUROC	95% CI	*p*-value	Cut-off*	Sensitivity (%)	Specificity (%)
Overall analysis						
CLIF-SOFA	0.750	0.62 to 0.88	0.001	8.5	70	70
CLIF/NGAL56	0.772	0.65 to 0.90	<0.001	9.5	75	72
CLIF/NGAL72	0.764	0.64 to 0.89	<0.001	9.5	75	74
MELD score	0.656	0.51 to 0.80	0.039	22.5	60	67
Subgroup analysis in non-AKI patients						
CLIF-SOFA	0.772	0.60 to 0.95	0.006	7.5	82	57
CLIF/NGAL56	0.783	0.60 to 0.96	0.004	8.5	82	71
CLIF/NGAL72	0.776	0.60 to 0.96	0.005	8.5	82	73
MELD score	0.559	0.37 to 0.75	0.549	17.0	55	50

ACLF = acute-on-chronic liver failure; AKI = acute kidney injury; AUROC = area under ROC curve; CI = confidence interval

* Best cut-off score

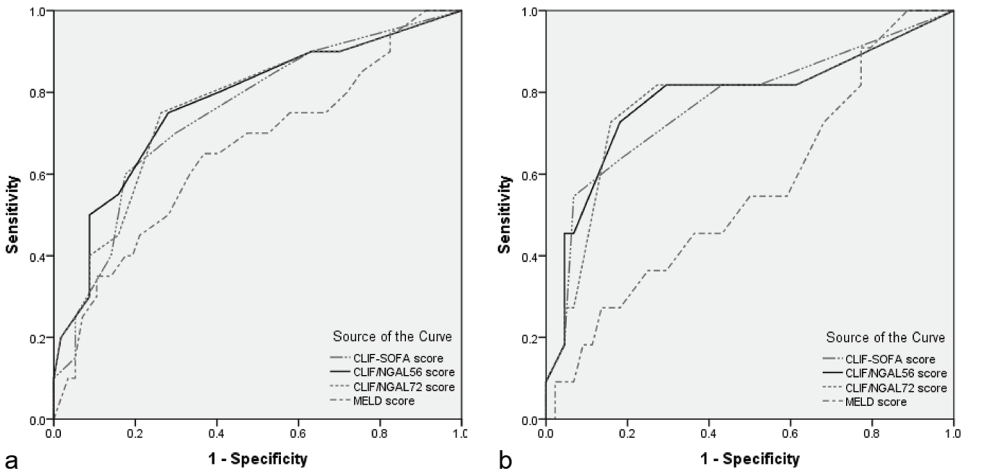

Figure 3. Mortality prediction accuracy among the ACLF patients who were diagnosed by different diagnostic scores, (a) overall analysis and (b) non-AKI subgroup analysis.

than other available scoring systems[8,9]. Despite extensive evaluation, the few studies that have been conducted in Asian countries have included relatively small sample sizes.

Shalimar et al[6] investigated predictors of mortality in ACLF patients and found that, in addition to the number and type of organ failures, the precipitating factor also had an influence on mortality. Alcohol consumption and chronic HBV or HCV infection were the major causes of cirrhosis in the present report, which seemed compatible with other Asian studies[10-14]. Furthermore, the present study was the first to investigate the effect of single and mixed cirrhotic etiologies on the prognosis of ACLF patients. Because Thailand has an extremely high alcohol consumption rate with also high prevalence of HBV and HCV infections, these mixed etiologies were very common and responsible for 18.6% of the cases in the present study population. Patients with mixed cirrhotic etiologies in both the overall and ACLF-subgroup analyses had higher odd ratios compared to the subjects with a single cause, but these differences did not reach significance (i.e., the 95% CI was too wide to conclude no effect). NAFLD had the highest OR in ACLF, but it should be noted that the number of patients in this group was extremely low (Table 2). Regarding the ACLF prognosis, patients with bacterial infections and drug-induced liver injuries were at increased risk of death; however, only the latter reached statistical significance. The outcome from the present study and the study of Shalimar et al[6] suggested that the cirrhotic etiology and aggravating factors might have some influence on ACLF prognosis, although the exact influential factors could not be concluded due to inconsistent results between these papers. The authors believe that the small number of patients in each group affected the ability to precisely predict the true effect of individual factors.

A prospective study by Shalimar et al and a large retrospective cohort study by Zang et al[15] showed that ACLF patients with serum creatinine levels greater than 1.5 mg/dL had an increased risk of death. Although renal dysfunction was clearly a strong mortality predictor in hospitalized cirrhotic patients, Angeli et al[16] demonstrated that the ACLF diagnosis using the CLIF-SOFA score still predicted mortality more precisely than the use of serum creatinine alone. Notably, the ACLF assessment from the study of Angeli et al, which used either the CLIF-SOFA score or the AKI classification at 48 hours, was significantly more accurate than the assessment at study enrollment. The rise in the serum creatinine level from the time of onset of kidney injury until reaching a detectable level is usually 24 to 48 hours[3]. This gap causes a delay in kidney injury detection and may explain why the ACLF assessment at 48 hours is more accurate.

Among the available biomarkers for renal injury, uNGAL is currently available in the authors' hospital service and has been the most validated biomarker for clinical applications. In animal models, uNGAL can be detected within 2 to 4 hours after the onset of kidney injury and has been applied for early renal injury detection in many circumstances, such as sepsis, contrast-induced nephropathy, cardiorenal syndrome, and hepatorenal syndrome[17]. Thus, uNGAL is a good option for application with the current criteria to

improve the sensitivity of ACLF detection.

In the present study validation of the CLIF-SOFA score, the ACLF patients had significant higher 1-month MRs than the patients without ACLF (43.7% versus 13.3%), which was in agreement with the ACLF definition and the MR from the CANONIC study. The AUROC for the CLIF-SOFA score was 0.750 (95% CI 0.62 to 0.88, $p = 0.001$), with a sensitivity of 70% and specificity of 70%. The present study AUROC was slightly lower than the value reported by Dhiman et al[13] (AUROC 0.795) but was moderately lower than the value reported by Silva et al[9] (AUROC 0.847). The difference might be related to the study population and ACLF etiologies. Each criterion from the present study had the same tendency as the CANONIC study and other publications from Asia[6,10-14] in which the higher grading correlated with a greater MR. However, the non-ACLF MR from the present study was rather high. Bacterial infection, which was the main precipitating factor, might explain this finding because sepsis had a considerably high MR by itself, which was independent of the host status.

Regarding the prognostic value of each criterion, the MELD score had the lowest correlation with the mortality prediction. Patients with an uNGAL level greater than both cut-off criteria were significantly associated with higher mortality. The findings were similar to the recent publication by Ariza et al[18], which was the first study to investigate uNGAL and ACLF patients. The authors analyzed plasma and urine NGAL levels from subjects in the CANONIC study and found that the uNGAL level was markedly elevated in the ACLF patients and non-survivors. The combination of the uNGAL level and the MELD score could also improve the prediction accuracy. These results supported the present study hypothesis that uNGAL had the potential to promote the sensitivity of the CLIF-SOFA score for earlier ACLF detection.

The present study results confirmed the study's hypothesis. The combination of CLIF/NGAL56 criteria had the highest OR compared to the other scores. Based on the sensitivity and specificity assessment by the ROC curves, the CLIF-SOFA and CLIF/NGAL scores represented fair diagnostic tests (AUROCs between 0.7 and 0.8), whereas the MELD score seemed to be a poor test (AUROC of 0.66). Both the CLIF/NGAL scores had AUROCs superior to the CLIF-SOFA and MELD scores. From the present study, the CLIF/NGAL56 score demonstrated the potential to be the best screening criterion for the ACLF diagnosis in terms of mortality prediction. However, the uNGAL cut-off level had a strong influence on the prognosis prediction, as shown by the uNGAL72 criteria, and had a lower OR than the uNGAL56 criterion. Additionally, the CLIF/NGAL72 score had a poorer predictive value than the CLIF/NGAL56 and CLIF-SOFA scores.

The benefit of the combination criteria was also observed in the subgroup analysis in non-AKI patients. The outcomes were similar to those obtained in the overall analysis. In the ACLF patients, the CLIF/NGAL56 score was associated with the worst prognosis, followed by the CLIF/NGAL72 score and the CLIF-SOFA score. Moreover, the sensitivity and specificity of each score in the non-AKI subgroup were slightly greater than the measurements for the overall cases. One advantage is that the high sensitivity CLIF/NGAL score can be applied to ACLF-prone patients who do not meet any organ failure criteria based on the original CLIF-SOFA score, which may exclude them from the ACLF diagnosis.

The present study had some limitations. According to our results, the uNGAL cut-off level considerably influenced the prediction ability, with a lower cut-off level most likely to correlate with better sensitivity. Because the cut-off level used in the present study was based on the previous study with a relatively small sample size, an additional multi-center evaluation with a larger population size is required.

Conclusion

The CLIF-SOFA score is a valid criterion for the diagnosis of ACLF among Thai patients with cirrhosis. Patients who met the combination of the uNGAL and serum creatinine level criteria in the CLIF-SOFA score (CLIF/NGAL score) were associated with a higher MR compared to the use of the CLIF-SOFA score alone. The prognostic prediction benefits of the CLIF/NGAL score could be applied to both AKI and non-AKI cirrhosis patients. Therefore, the CLIF/NGAL score is potentially superior to the use of the CLIF-SOFA score alone for ACLF detection.

What is already known on this topic?

The CLIF-SOFA score has been the most accepted criterion in mortality prediction in ACLF patients. Urine NGAL is more sensitive than serum creatinine in the detection of renal failure, which is the major organ related to ACLF prognosis.

What this study adds?

The CLIF/NGAL score is superior to the CLIF-SOFA score alone in the prediction of mortality among

ACLF patients.

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Potential conflicts of interest

The authors declare no conflict of interest.

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