Prognostic study of acute-on-chronic liver failure patients
Usefulness of the fibrosis-4 index

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Abstract
Acute-on-chronic liver failure (ACLF) is a syndrome characterized by an acute deterioration of liver function in cirrhotic patients. Since treatment of this condition is difficult, its prevention is of paramount importance. The predictors of ACLF are yet to be identified. To determine the prognosis of cirrhotic and ACLF patients, we conducted a retrospective study to analyze each parameter in ACLF patients.

Cirrhotic patients with serum total-bilirubin level ≥5.0 mg/dL and prothrombin time (PT) value ≤40% after acute insults were diagnosed with ACLF, whereas patients who met one of the above criteria were diagnosed with extended type of ACLF (EX-ACLF). Overall, in this study, 18 ACLF and 16 EX-ACLF patients retrospectively investigated between 2008 and 2020, and each data was analyzed during and before acute insults.

In the analysis during acute insults, renal and coagulation functions showed significant differences between the ACLF and EX-ACLF groups. Furthermore, the mortality rate in the ACLF group was higher than that in the EX-ACLF group. In the analysis before acute insults, aspartate aminotransferase (AST), Fibrosis-4 (FIB-4) index score, and AST to platelet ratio index (APRI) showed significant differences between the two groups. Among these, the FIB-4 index score correlated best with ACLF severity for identifying cirrhotic patients with poor prognosis.

The FIB-4 index is the most useful predictor of ACLF severity. Careful management of cirrhotic patients with a high FIB-4 index score is considered beneficial to prevent ACLF occurrence.

Abbreviations: ACLF = acute-on-chronic liver failure, APASL = Asian Pacific Association for the Study of the Liver, APRI = AST to platelet ratio index, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, AUROC = area under the ROC, BUN = blood urea nitrogen, CLIF-C = chronic liver failure consortium, CPS = Child-Pugh score, Cre = creatinine, CRP = c-reactive protein; D-D, D-dimer, EX-ACLF = extended type of acute-on-chronic liver failure, FDP = fibrin/fibrinogen degradation products, Fib = fibrinogen; FIB-4 = Fibrosis-4, MELD = model for end-stage liver disease, Plt = platelet count, PT = prothrombin time, ROC = receiver operating characteristic, Rs = correlation coefficient, T-bil = total-bilirubin.

Keywords: acute on chronic liver failure, cirrhosis, fibrosis-4 index

1. Introduction
Acute-on-chronic liver failure (ACLF) is a syndrome characterized by an acute deterioration of liver function in cirrhotic patients, progressing to severe liver failure in a short period caused by acute insults such as exacerbation of underlying liver disease, variceal rupture, alcohol abuse, infections, and sepsis.[1,2] Once ACLF is diagnosed, it requires intensive care and organ support[1,3] and often leads to severe condition with high mortality rate (60%–90%).[4,5] Despite the advancement in medicine, supportive care is the main treatment for ACLF patients.[5] Liver transplantation is an available treatment option for ACLF; however, only few patients can actually receive a liver transplantation due to the shortage of donors or invasiveness of transplant surgery.[6] Even with liver transplantation, the survival rate for ACLF patients is not high.[7] Since ACLF has a poor prognosis and is mainly treated with supportive care, the best way for patients is to prevent ACLF occurrence, or to prevent acute insults. In previous reports, predictors of ACLF occurrence have not been identified yet and further validation is required.
In previous studies, we have analyzed ACLF with poor prognosis. The analysis included ACLF patients with serum total-bilirubin level (T-bil) ≥ 5.0 mg/dL and prothrombin time (PT) value ≤ 40% after acute insults (the group meeting the ACLF criteria: the ACLF group) and patients with serum T-bil ≥ 5.0 mg/dL or PT value ≤ 40% after acute insults (the group with extended type of ACLF: the EX-ACLF group). Based on this previous study, we analyzed patients in the ACLF and EX-ACLF groups of our hospital and in a cooperating institution to identify prognosis-related factors in cirrhotic and ACLF patients.

2. Methods

2.1. Patients

ACLF and EX-ACLF patients admitted to the Niigata University (Niigata, Japan) and the Niigata City General Hospital (Niigata, Japan) between April 2008 and April 2020 were retrospectively investigated. ACLF was diagnosed based on the following criteria for ACLF in Japan: Patients with cirrhosis and a Child-Pugh score (CPS) of 5 to 9 points should be diagnosed with ACLF when a deterioration of liver function (serum T-bil ≥ 5.0 mg/dL and PT value ≤ 40% of the standardized values) caused by severe liver damage develops within 28 days after acute insults, such as alcohol abuse, bacterial infection, gastrointestinal bleeding, or the exacerbation of underlying liver disease (Table 1). On the contrary, EX-ACLF was diagnosed based on the lenient criteria of ACLF: Patients with cirrhosis and a CPS of 5 to 9 points should be diagnosed with ACLF when deterioration of liver function (serum T-bil ≥ 5.0 mg/dL or PT value ≤ 40% of the standardized values) caused by severe liver damage develops within 28 days after acute insults. The Spearman rank correlation test was conducted to determine the correlation between the severity grade of ACLF and clinical parameters.

2.2. Data collection

All patients included in the study were investigated for their medical history, including age, gender, etiology of liver disease, and type of acute insults. In laboratory examinations, during and before acute insults, levels of T-bil, albumin, creatinine (Cre), white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count (Plt), creatinine kinase, aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl-transpeptidase, cholinesterase, blood urea nitrogen (BUN), sodium, potassium, chlorine (Cl), C-reactive protein (CRP), ammonia, fasting blood sugar, PT (PT/sec, PT-INR, PT%), activated partial thromboplastin time (APTT), fibrinogen (Fib), fibrin/fibrinogen degradation products (FDP), D-dimer (D-D), and antithrombin III were measured at each hospital. To predict ACLF occurrence, data were selected up to 6 months before the acute insults. From these data, the CPS,[9] model for end-stage liver disease (MELD) score,[10] albumin-bilirubin score,[11] Fibrosis-4 (FIB-4) index score,[12] AST to Plt ratio index (APRI) score,[13] and Chronic Liver Failure Consortium (CLIF-C)[14] score were calculated as previously described.

3. Results

3.1. Clinical characteristics during acute insults

A total of 34 patients, 18 with ACLF and 16 with EX-ACLF, were retrospectively investigated in this study (Table 1). The characteristics of the patients' background showed no statistical differences between the two groups; however, the most common etiology of liver disease was alcoholic cirrhosis, and the most common acute insult was gastrointestinal bleeding in both groups (Table 2). The parameters during acute insults showed significant differences in BUN, Cre, CRP, PT (seconds), PT-INR, PT (%), APTT, FDP, D-D, and CLIF-C scores between ACLF and EX-ACLF patients (Table 3).

3.2. Outcome of ACLF and extended type of ACLF

Only 1 out of 16 patients (6.3%) died in the EX-ACLF group. In contrast, 15 of 18 patients (83.3%) died in the ACLF group, showing that the mortality rate of ACLF was higher than that of EX-ACLF (Fig. 1).

3.3. Predictive factors for ACLF occurrence (clinical characteristics before acute insults)

Once ACLF is observed, the prognosis is extremely poor, with a high mortality rate. Since ACLF has a poor prognosis and is mainly treated with supportive care, the best way for patients is to prevent acute insults. Therefore, the data before acute insults were analyzed to identify the parameters for predicting ACLF occurrence. The data before acute insults showed significant differences between the two groups in AST, FIB-4 index, and APRI scores (Table 4). These three parameters could be predictors of ACLF.

3.4. Further analysis of predictive factors (AST, FIB-4 index, and AST to platelet ratio index (APRI))

Further analysis was performed on three parameters before acute insults, including AST, FIB-4 index, and APRI scores, to make these data more accurate. To analyze the correlation

Table 1

| Definition of ACLF and EX-ACLF. |
|----------------------------------|
| ACLF | T-bil ≥ 5.0 mg/dL and PT value ≤ 40% after acute insults |
| EX-ACLF | T-bil ≥ 5.0 mg/dL or PT value ≤ 40% after acute insults |

ACLF = acute-on-chronic liver failure, EX-ACLF = extended type of acute-on-chronic liver failure, T-bil = total-bilirubin, PT = prothrombin time.
Regarding AST, no significant correlation was found between AST and CLIF-C (correlation coefficient: Rs = 0.203, P = 0.261). Regarding the FIB-4 index and APRI, a significant positive correlation was observed (Rs = 0.764, P < .001, Rs = 0.367, P = 0.043, respectively), and the Rs of the FIB-4 index was higher than those of other parameters (Fig. 2). These results suggest that FIB-4 index correlates best with the severity of ACLF. Furthermore, ROC analysis was performed to predict the occurrence of ACLF. All data provided significant predictive values, with AUROC for AST, FIB-4 index, and APRI of 0.713, 0.879, and 0.688, respectively. However, the FIB-4 index had a significant predictive value compared to the others. The cutoff value of AST was 45 IU/L (sensitivity: 0.94, specificity: 0.50); the FIB-4 index was 4.22 (sensitivity: 0.88, specificity: 0.87), and that of APRI was 2.18 (sensitivity: 0.65, specificity: 0.81) (Fig. 3).

4. Discussion

From 2008 to 2020, 18 ACLF and 16 EX-ACLF patients were diagnosed at our institution. Although ACLF is a rare disease, it should be noted that once diagnosed, its mortality rate is high. In our study, alcoholic cirrhosis was the most common background liver disease in ACLF patients. However, the etiology of ACLF is diverse, and it has been reported that the background liver

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### Table 2
Clinical characteristics of ACLF and EX-ACLF patients.

| Parameter                  | ACLF (n = 18) | EX-ACLF (n = 16) | P-value |
|----------------------------|---------------|-----------------|---------|
| Gender                     |               |                 |         |
| Male                       | 11            | 7               |         |
| Female                     | 7             | 9               |         |
| Etiology                   |               |                 |         |
| HBV infection              | 3             | 0               |         |
| HCV infection              | 0             | 0               |         |
| Alcoholic                  | 12            | 11              |         |
| Nonalcoholic               | 0             | 2               |         |
| Autoimmune                 | 3             | 3               |         |
| Primary biliary cholangitis| 0             | 0               |         |
| Cause of acute insult      |               |                 |         |
| Gastrointestinal bleeding  | 6             | 7               |         |
| Infection                  | 4             | 2               |         |
| Alcohol abuse              | 3             | 5               |         |
| Exacerbation of hepatitis  | 5             | 2               |         |

ACLF = acute-on-chronic liver failure, EX-ACLF = extended type of acute-on-chronic liver failure, HBV = hepatitis B virus, HCV = hepatitis C virus.

### Table 3
Parameters of ACLF and EX-ACLF patients during acute insults.

| Parameter                  | ACLF (n = 18) | EX-ACLF (n = 16) | P-value |
|----------------------------|---------------|-----------------|---------|
| Age (years)                | 59 (29-70)    | 58 (33-80)      | .918    |
| T-Bil (mg/dL)              | 10.2 (5.4-29.5)| 8.3 (1.5-17.7)  | .068    |
| Alb (g/dL)                 | 2.4 (1.5-3.3) | 2.5 (1.5-3.1)   | .014    |
| AST (IU/L)                 | 199 (57-2589) | 191 (49-2751)   | .914    |
| ALT (IU/L)                 | 94 (29-2944)  | 55 (20-1621)    | .139    |
| ALP (IU/L)                 | 440 (186-644) | 560 (359-632)   | .181    |
| LDH (IU/L)                 | 436 (208-4210)| 368 (164-1737)  | .416    |
| γ-GTP (IU/L)               | 125 (17-514)  | 338 (38-1286)   | .081    |
| CHE (IU/L)                 | 71 (30-162)   | 119 (43-228)    | .057    |
| BUN (mg/dL)                | 22.2 (6.0-137) | 8.6 (2.9-36.0)  | .06*    |
|cre (mg/dL)                 | 0.94 (0.53-4.48)| 0.65 (0.33-1.73)| .039*   |
| NH3 (µg/dL)                | 121 (48-206)  | 91 (25-153)     | .068    |
| CK (µL)                    | 170 (30-2472) | 75 (24-1173)    | .072    |
| FBS (mg/dL)                | 117 (20-309)  | 115 (84-168)    | .731    |
| CRP (mg/dL)                | 3.44 (0.63-22.93)| 1.47 (0.29-3.03)| .022*   |
| Na (mmol/L)                | 133 (121-153) | 135 (113-147)   | .374    |
| K (mmol/L)                 | 4.0 (1.6-5.8) | 3.4 (2.5-5.3)   | .192    |
| Cl (mmol/L)                | 97 (82-122)   | 101 (69-108)    | .815    |
| WBC (×10^9/L)              | 1.06 (0.40-3.71)| 0.78 (0.48-2.54)| .055    |
| RBC (×10^12/L)             | 2.96 (1.43-4.61)| 3.03 (2.08-5.11)| .665    |
| Hct (%)                    | 29.3 (15.2-42.2)| 30.5 (19.5-51.4)| .718    |
| Pit (×10^9/L)              | 9.4 (1.4-27.8) | 13.7 (3.4-25.3) | .679    |
| PT (seconds)               | 20.2 (18.2-43.3)| 17.2 (13.3-22.2)| <.001** |
| PT-INR                     | 1.80 (1.54-3.60)| 1.51 (1.9-21.11)| <.001** |
| PT (%)                     | 33 (13-44)    | 45 (44-70)      | <.001** |
| APTT (seconds)             | 45.7 (36.1-64.2)| 37.4 (26.1-53.9)| .005** |
| Fbg (mg/dL)                | 148 (73-348)  | 152 (84-226)    | .591    |
| FDP (µg/mL)                | 19.4 (3.0-69.3)| 2.4 (1.1-15.4)  | .008**  |
| D-D (µg/mL)                | 10.4 (1.0-32.9)| 2.9 (0.5-21.2)  | .011*   |
| AT-III (%)                 | 25 (16-42)    | 41 (27-54)      | .062    |
| CLIF-C score               | 51.9 (31.8-64.1) | 36.9 (25.7-59.6) | <.001** |

All data represents median and range
* P < .05
** P < .01.

ACLF = acute-on-chronic liver failure, ALP = alkaline phosphatase, Alb = albumin, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, AT III = antithrombin III, BUN = blood urea nitrogen, CHE = cholinesterase, CK = creatine kinase, Cl = chloride, CLIF-C = Chronic Liver Failure Consortium, Cre = creatinine, CRP = C-reactive protein, D-D = D-dimer, EX-ACLF = extended type of acute-on-chronic liver failure, FDP = fibrin/fibrinogen degradation products, FBS = fasting blood sugar, Fbg = fibrinogen, γ-GTP = gamma-glutamyl-transpeptidase, Hb = hemoglobin, Hct = hematocrit, K = potassium, LDH = lactate dehydrogenase, Na = sodium, NH3 = ammonia, Plt = platelet, PT = prothrombin time, T-Bil = total bilirubin, ABC = red blood cell count, WBC = white blood cell count.
disease has regional differences.\cite{11,12} Gastrointestinal bleeding is a serious complication of ACLF and can be an acute insult.\cite{16,17}

In this study, the most common acute insult was gastrointestinal bleeding. For cirrhotic patients, it is necessary to take prophylactic oral administration of proton pump inhibitors for mucosal disorders, to avoid oral administration of non-steroidal anti-inflammatory drugs, and to manage gastrointestinal varices. From the data obtained during acute insults, significant differences were observed in BUN and Cre between ACLF and EX-ACLF patients, and it is considered that renal function was worse in the ACLF group than that in the EX-ACLF group. Cre was selected as a scoring factor in the Japan Severity ACLF classification.\cite{19} Asian Pacific Association for the Study of the Liver (APASL), ACLF Research Consortium (ACLF severity score proposed by the APASL),\cite{20} and CLIF-C (ACLF severity score proposed by the European Association for the Study of the Liver).\cite{21,22} Recent reports suggested that on line hemodiafiltration with high dialysate flow rate is effective in preventing and improving encephalopathy in acute liver failure, and is expected to have the same effect on ACLF.\cite{23} Based on the data before acute insults, significant differences were also observed in PT (seconds), PT-INR, PT (%), APTT, FDP, and D-D between the two groups, suggesting that coagulation function was worse in the ACLF group than in the EX-ACLF group. Coagulation and renal functions were selected

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{mortality_rate.png}
\caption{The mortality rate of ACLF and EX-ACLF. Data are presented as percent of patients with death outcomes out of the total number of patients. ACLF = acute-on-chronic liver failure, EX-ACLF = extended type of acute-on-chronic liver failure.}
\end{figure}

\begin{table}[h]
\centering
\caption{Parameters of ACLF and EX-ACLF patients before acute insults.}
\begin{tabular}{llll}
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Parameter      & ACLF (n = 18) & EX-ACLF (n = 16) & P-value  \\
\hline
Age (years)    & 59 (29-78)   & 58 (33-80)   & .576     \\
T-Bil (mg/dL)  & 1.4 (0.5-3.2) & 1.3 (0.2-3.8) & .914     \\
Alb (g/dL)     & 3.4 (2.5-4.8) & 3.5 (2.3-4.5) & .800     \\
AST (U/L)      & 91 (32-163)  & 48 (12-128)  & .037*    \\
ALT (U/L)      & 48 (19-156)  & 33 (6-87)    & .071     \\
ALP (U/L)      & 400 (178-1250) & 367 (175-1328) & .914     \\
LDH (U/L)      & 255 (140-382) & 204 (148-562) & .189     \\
γ-GTP (U/L)    & 150 (94-338) & 100 (19-1263) & .601     \\
CH E (U/L)     & 16.0 (3.5-49.1) & 169 (87-291) & .349     \\
BUN (mg/dL)    & 0.81 (0.43-2.06) & 9.3 (0-25.4) & .063     \\
Cre (mg/dL)    & 0.20 (0.01-1.12) & 0.59 (0.47-0.88) & .067     \\
CRP (mg/dL)    & 0.88 (0.80-1.36) & .801     \\
Na (mmol/L)    & 140 (135-146) & 139 (135-146) & .827     \\
K (mmol/L)     & 4.0 (3.3-4.4) & 3.9 (2.8-4.7) & .538     \\
Cl (mmol/L)    & 104 (96-110) & 103 (91-111) & .957     \\
WBC (×103/µL) & 0.61 (0.23-0.96) & 0.52 (0.46-0.88) & .815     \\
RBC (×1012/µL) & 3.16 (1.91-4.59) & 3.34 (2.72-4.89) & .596     \\
Hct (%)        & 10.4 (6.3-16.1) & 11.4 (9.3-17.0) & .135     \\
Hct (%)        & 31.8 (19.8-45.4) & 34.1 (29.7-48.4) & .064     \\
Pit (×10³/µL)  & 11.5 (5.1-20.7) & 14.0 (7.1-24.1) & .052     \\
PT (seconds)   & 13.2 (11.3-16.6) & 13.0 (10.6-14.5) & .313     \\
PT-INR         & 1.18 (1.10-1.41) & 1.15 (0.95-1.37) & .117     \\
PT %           & 71 (49-89) & 76 (54-113) & .165     \\
MELD score     & 31.6 (23.9-44.1) & 30.0 (26.8-39.6) & .296     \\
Child-Pugh score & 7 (5-9) & 7 (5-9) & .351     \\
MELD score     & 10 (8-20) & 9 (6-16) & .205     \\
ALB score      & -2.00 (-3.11--1.02) & -2.14 (-3.04--0.76) & .801     \\
FIB-4 Index    & 6.57 (3.24-14.87) & 2.67 (1.01-8.68) & .005**    \\
APRI           & 2.47 (1.08-6.53) & 1.58 (0.71-4.82) & .043*     \\
\hline
\end{tabular}
\end{table}

All data represents median and range

* P < .05,
** P < .01.

ACLF = acute-on-chronic liver failure, ALBI = albumin-bilirubin, Alb = albumin, ALT = alanine aminotransferase, ALP = alkaline phosphatase, APRI = AST to platelet ratio index, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, Cl = chlorine, CH E = cholinesterase, Cre = creatinine; CRP = C-reactive protein, EX-ACLF = extended type of acute-on-chronic liver failure, Na = sodium, Pit = platelet, PT = prothrombin time, RBC = red blood cell count, T-bil = total bilirubin, WBC = white blood cell count.
Figure 2. Spearman rank correlation test of AST, FIB-4 index, and APRI. The FIB-4 index showed the best correlation with the score of CLIF-C. AST = aspartate aminotransferase, APRI = AST to platelet ratio index, CLIF-C = Chronic Liver Failure Consortium, FIB-4 = Fibrosis-4.

Figure 3. ROC of AST, FIB-4 index, and APRI. Based on the AUROC, the FIB-4 index is determined to be the most useful predictor of ACLF occurrence. From ROC analysis, the cutoff value, sensitivity, specificity, PPV, and NPV were calculated. ACLF = acute-on-chronic liver failure, AST = aspartate aminotransferase, APRI = AST to platelet ratio index, AUROC = area under the ROC, FIB-4 = Fibrosis-4, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic curves.
as scoring factors. This is consistent with the results of the present analysis. Furthermore, thromboembolism (i.e., pulmonary embolism) associated with coagulation deterioration is one of the causes of death in ACLF patients, and it is necessary to manage the patients to prevent dehydration. Although the difference between the definitions of ACLF (PT < 40% and T-Bil > 5.0 mg/dL) and EX-ACLF (PT < 40% or T-Bil > 5.0 mg/dL) is small, there is a large difference in their mortality rates, demonstrating that the ACLF criteria are useful. In other words, the prognosis depends on whether the patient is diagnosed with ACLF or EX-ACLF. To improve the prognosis of cirrhotic patients, it is important to prevent acute insults or to stop within the range of EX-ACLF even if acute insults occur. Therefore, to identify factors associated with ACLF occurrence, analysis, using data before acute insults, would be necessary. The data before acute insults showed significant differences in AST, FIB-4 index, and APRI scores between the two groups. In the Spearman rank correlation test, the severity score (CLIF-C) was strongly correlated with the FIB-4 index, suggesting that the Spearman rank correlation test, the severity score (CLIF-C) in patients with an FIB-4 index > 4.22 before acute insult should be paid attention for ACLF occurrence.

According to previous reports, the FIB-4 index is an indicator of liver fibrosis. Based on the results of this study, cirrhosis with more advanced fibrosis is more likely to occur severe ACLF. To hypothesize the mechanism of ACLF, in cirrhosis with more advanced liver fibrosis, the function is maintained with fewer residual hepatocytes. However, acute insults easily cause functional failure. Furthermore, more advanced fibrosis leads to progression of cirrhosis and then occurs portal hypertension, resulting in gastrointestinal varices and portal hypertensive gastroenteropathy. Gastrointestinal bleeding is a common acute insult. Asceres caused by portal hypertension leads to spontaneous bacterial peritonitis, resulting in an acute insult. As a measure to prevent ACLF, if the FIB-4 index score is high (specifically ≥ 4.22 or over), examination with gastrointestinal endoscopy or computed tomography to avoid acute insults is important. In addition, regenerative therapy to reduce liver fibrosis has been actively conducted recently. Although regenerative therapy is still in the preclinical stage, if realized, it would contribute to the prevention of ACLF. Certainly, since this was a retrospective study limited to patients diagnosed with ACLF or EX-ACLF, the results of this study would not be suitable for all cirrhotic patients. Accumulation of cases and prospective studies are future tasks. However, all cirrhotic patients are at risk of ACLF, and management according to the results of this analysis would be of sufficient benefit.

In conclusion, the FIB-4 index is the most useful predictor of ACLF and may contribute to improving the prognosis of cirrhotic patients. Careful management of patients with a high FIB-4 index score may benefit cirrhotic patients.

**Author contributions**

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