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Long-term Prognosis of Acute-on-Chronic Liver Failure Survivors

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Goals: We aimed to investigate significant factors influencing the long-term prognosis of patients who survived acute-on-chronic liver failure (ACLF).

Background: The mortality of ACLF is predominantly affected by the organ failure severity. However, long-term outcomes of patients who survive ACLF are not known.

Study: A cohort of 1084 cirrhotic patients who survived for more than 3 months following acute deterioration of liver function was prospectively followed. ACLF was defined by the European Association for the Study of the Liver Chronic Liver Failure Consortium definition.

Results: The mean follow-up duration was 19.4 ± 9.9 months. In the subgroup of patients without previous acute decompensation (AD), ACLF occurrence did not affect long-term outcomes. However, in patients with previous AD, ACLF negatively affected long-term transplant-free survival even after overcoming ACLF (hazard ratio, 2.00, $P = 0.012$). Previous AD was the significant predictive factor of long-term mortality and was independent of the Model for End-stage Liver Disease score in these ACLF-surviving patients. Organ failure severity did not affect transplant-free survival in patients who survived an ACLF episode.

Conclusions: A prior history of AD is the most important factor affecting long-term outcomes following an ACLF episode regardless of Model for End-stage Liver Disease score. Prevention of a first AD episode may improve the long-term transplant-free survival of liver cirrhosis patients.

Key Words: acute-on-chronic liver failure, decompensation, organ failure, survival

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Acute-on-chronic liver failure (ACLF) is a distinct disease entity in patients with chronic liver disease (CLD). Recently, the European Association for the Study of the Liver Chronic Liver Failure Consortium (EASL CLIF-C) defined ACLF as a syndrome characterized by organ failure and high short-term mortality in the setting of acute decompensation (AD) of cirrhosis from the Chronic Liver Failure Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study.[1] Recent data from Korea show that the short-term mortality of ACLF was nearly 30% within 28 days and increased to 50% within 90 days after ACLF.[1–3] In an extension of the CANONIC study, Jalan et al[4]

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reported 6-month and 1-year mortality as 52.0% and 57.8%, respectively. In addition, Bruno et al[5] showed that ACLF was the most significant clinical predictor of the poorest outcome in a 3-year follow-up period, with mortality reaching 62%. Therefore, the development of ACLF and the organ failure severity are clearly the most significant factors affecting mortality rates in liver cirrhosis patients. The CLIF Consortium ACLF score (CLIF-C ACLFs), which has been proposed to determine prognosis in this setting, is determined by the overall organ failure severity [based on the CLIF-sequential organ failure assessment (CLIF-SOFA) score], age, and white blood cell count (WBC).[5] The organ failure severity and WBC generally reflect acute damage from ACLF. Whether these acute injuries affect the long-term prognosis of patients who survive ACLF is not known.[6,7] Therefore, we aimed to investigate the factors affecting the long-term prognosis in patients who survived for >3 months following ACLF.

Furthermore, a history of previous AD implies the occurrence of decompensated liver cirrhosis. Whether the ACLF event is the first episode of AD or not may be directly related to the outcome following ACLF. Therefore, we also focused on the effects of previous AD on the long-term prognosis in this population.

MATERIALS AND METHODS

Patients

The Korean Acute-on-Chronic Liver Failure (KACLiF) cohort consisted of 1470 patients who were hospitalized with acute deterioration of CLD, including either liver cirrhosis or noncirrhotic CLD, from January 2013 to December 2013. Survival data of these patients were prospectively collected until September 2015. This study was approved by the Institutional Review Board of all the participating centers. In the KACLiF study, acute deterioration was defined as overt ascites, hepatic encephalopathy, gastrointestinal bleeding (including variceal bleeding), bacterial infection, and liver dysfunction, which was defined as a serum bilirubin level ≥3 mg/dL. This definition was adapted from the CLIF-C definition. The condition of "liver dysfunction" was added to the definition so as to not miss patients who would suffer ACLF in the near future. Patients without evidence of liver cirrhosis were excluded based on the CLIF-C criteria. Among the 1352 cirrhotic patients, 274 patients met the criteria for ACLF within 1 month of enrollment. Among these ACLF patients, 22 patients and 134 patients were lost during follow-up or died within 3 months, respectively. In addition, among the patients without ACLF, 75 patients and 37 patients were lost to follow-up or died within 3 months, respectively (Fig. 1). AD was defined as the occurrence of jaundice (serum bilirubin level, ≥3 mg/dL) and/or portal hypertensive complications, such as variceal bleeding, ascites, or hepatic encephalopathy. These ADs, different from the acute deterioration described above, focused on hepatic insults, as adapted and modified from Asian Pacific Association for the study of liver ACLF Research Consortium definition. Therefore, prior AD was defined as hepatic insults and/or jaundice that had been developed prior to the index event of acute deterioration.[8] Patients who underwent liver transplantation were censored.

Study Endpoints

The primary endpoint of this study was to assess the impact of ACLF on the long-term outcome of patients who survived for >3 months following ACLF. The secondary endpoint was to identify factors other than ACLF that may influence long-term transplant-free survival after ACLF recovery. Survival from ACLF was arbitrarily defined as survival exceeding 3 months following the index ACLF event based on data of Gustot et al[9] that 90- and 180-day mortalities of ACLF patients are not different in each grade of ACLF.

Statistical Analysis

Categorical variables and continuous variables are expressed as the mean ± SD and number (%), respectively. These variables were analyzed using the χ^2 test or the Fisher exact test and the Student independent t test, respectively. The transplant-free survival was calculated by the Kaplan-Meier method using a log-rank test. To assess the prognostic predictors affecting long-term transplant-free survival after

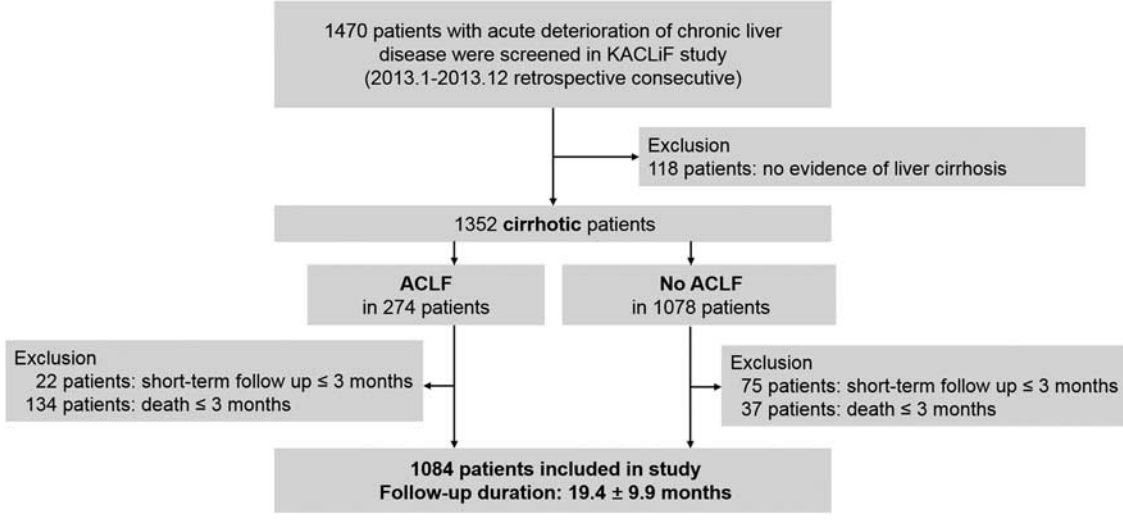

FIGURE 1. Flow chart of patients enrolled in the study. Data from 1352 cirrhotic patients were collected, and the patients were prospectively followed. Among them, 274 patients (20.2%) developed ACLF based on the European Association for the Study of the Liver Chronic Liver Failure Consortium definition. Excluding patients who were lost to follow-up or died within 3 months, a total of 1084 patients were included in this study, and the mean follow-up period was 19.4 months. ACLF indicates acute-on-chronic liver failure; KACLiF, Korean acute-on-chronic liver failure.

ACLF, the variables including sex, age, presence of previous AD, ACLF occurrences, WBC, C-reactive protein, albumin, total bilirubin, prothrombin time, creatinine, sodium, and Model for End-stage Liver Disease (MELD) score were used in the Cox regression models and hazard ratios of independent predictive factors. Significant variables by univariate analysis were subject to Cox multivariate regression. Statistical significance was set at a P-value <0.05. Statistical analysis was performed using SPSS 21.0 software (SPSS Inc., an IBM Company, Chicago, IL).

RESULTS

Baseline Characteristics

Of the 1084 patients included in this study, 802 patients were male (74.0%) (Table 1). The mean patient age was 56 years. The most common CLD etiology was alcohol use, and 63.6% of the patients included in the study used alcohol. Overt ascites and gastrointestinal bleeding were the dominant types of AD. Hepatic encephalopathy and bacterial infection were more prevalent in ACLF patients than in patients without ACLF. However, gastrointestinal bleeding was more prevalent in patients without ACLF. WBC and C-reactive protein values were higher in ACLF patients than in patients without ACLF. The ACLF groups had significantly lower albumin, higher bilirubin, and lower serum sodium levels and greater prothrombin time prolongation. The mean values of the clinical scores reflecting liver injury (Child-Turcotte-Pugh score, MELD score) and organ failure (eg, CLIF-SOFA score) indicated significantly worse status in the ACLF group.

TABLE 1. Baseline Characteristics of Cirrhotic Patients Who Survived 3 Months Following Acute Deterioration of Chronic Liver Disease (at Enrollment)

	All (N = 1084)	No ACLF (N = 966)	ACLF (N = 118)	P
Male	802 (74.0)	715 (74.0)	87 (73.7)	1.000
Age (y)*	56 ± 12	56 ± 12	56 ± 11	0.933
Etiology of CLD				
Viral	216 (19.9)	199 (20.6)	17 (14.4)	0.142
Alcohol	689 (63.6)	604 (62.5)	85 (72.0)	0.043
Viral+ alcohol	88 (8.1)	80 (8.3)	8 (6.8)	0.721
Others	91 (8.4)	83 (8.6)	8 (6.8)	0.600
Acute decompensation				
Ascites	371 (34.2)	325 (33.6)	46 (39.0)	0.259
HE	167 (15.4)	127 (13.1)	40 (33.9)	<0.001
GIB	489 (45.1)	454 (47.0)	35 (29.7)	<0.001
Infection	94 (8.7)	68 (7.0)	26 (22.0)	<0.001
WBC ($\times 10^9$/L)*	7.5 ± 4.6	7.3 ± 4.4	9.3 ± 5.6	<0.001
Platelets ($\times 10^9$/L)*	102 ± 60	104 ± 60	86 ± 55	0.003
Albumin (g/dL)*	2.9 ± 0.6	2.9 ± 0.6	2.7 ± 0.6	0.001
Bilirubin (mg/dL)*	3.9 ± 0.5	3.5 ± 4.3	7.2 ± 8.1	<0.001
Prothrombin time (INR)*	1.5 ± 0.3	1.4 ± 0.3	1.7 ± 0.6	<0.001
CRP (mg/L)*	3.0 ± 9.3	2.7 ± 8.5	5.8 ± 13.5	0.017
Creatinine (mg/dL)*	1.0 ± 1.0	0.9 ± 0.3	2.5 ± 2.5	<0.001
Sodium (mEq/L)*	136 ± 6	137 ± 5	133 ± 7	<0.001
Clinical scores				
CTP*	9 ± 2	8 ± 2	10 ± 2	<0.001
MELD*	15 ± 5	14 ± 4	23 ± 6	<0.001
CLIF-SOFA*	5 ± 2	4 ± 2	8 ± 3	<0.001

Categorical variables, shown as number of patients (percentage of patients), were analyzed using the χ^2 test or the Fisher exact test.

*Continuous variables, shown as the mean ± SD, were analyzed using the Student independent t test.

ACLF indicates acute-on-chronic liver failure; CLD, chronic liver disease; CLIF-SOFA, Chronic Liver Failure Consortium Sequential Organ Failure Assessment Score; CRP, C-reactive protein; CTP, Child-Turcotte-Pugh; GIB, gastrointestinal bleeding; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; WBC, white blood cell.

Long-term Prognosis of Patients Following ACLF

The mean follow-up period duration was 19.4 ± 9.9 months (Fig. 1). Eight patients underwent liver transplantation due to refractory cirrhosis complications during the follow-up. ACLF occurrence negatively affected long-term transplant-free survival regardless of previous AD in the survival analysis of patients who survived for >3 months following ACLF (Fig. 2A). The 1-year mortality of these patients differed according to previous ACLF, at 12.7% and 23.9% in patients without or with previous ACLF, respectively. The hazard ratio of previous ACLF in long-term mortality was 1.89 by Cox regression analysis [95% confidence interval (CI), 1.18-3.03. $P = 0.008$]. In the subgroup of patients without previous AD, the occurrence of ACLF did not affect the long-term prognosis (Fig. 2B). However, in patients with previous AD, ACLF occurrence negatively affected long-term transplant-free survival, even at 3 months following ACLF (hazard ratio, 2.00; 95% CI, 1.16-3.43; $P = 0.012$) (Fig. 2C).

Nevertheless, the MELD scores of patients without and with previous AD were 23 ± 6 and 23 ± 6 ($P = 0.554$), respectively. Organ failure severity graded by CLIF-SOFA also did not differ (8 ± 3 vs. 8 ± 3, $P = 0.948$) between these groups.

The survival curves of those who died within 3 months of ACLF were not affected by previous AD history ($P = 0.162$) (data not shown).

Common etiologies for mortality after ACLF were hepatic failure, gastrointestinal bleeding, infection, and sepsis.

Significant Predictors of Mortality in Cirrhosis Patients Who Survived ACLF

Because the long-term effects of ACLF differed depending on the history of previous AD, we analyzed whether previous AD was the main factor in predicting mortality among the patients who survived for more than 3 months following ACLF. In univariate analysis, older age, previous AD, ACLF occurrence, hypoalbuminemia, hyponatremia, and a high MELD score were significant predictors of mortality. In multivariate analysis, age, albumin, sodium, and MELD score, and previous AD were significant predictors of mortality in patients with cirrhosis. Among them, previous AD showed the highest hazard ratio of 1.89 (95% CI, 1.44-2.49; $P < 0.001$) (Table 2). Interestingly, ACLF occurrence was not a significant factor for long-term prognosis in patients who survived for >3 months following ACLF.

Long-term Effects of Organ Failure Severity in Subgroups Without or With Previous AD

In the subgroup of patients without previous AD, the 1-year mortalities were 7.8%, 15.0%, and 11.1% in patients without ACLF, grade 1 ACLF, and grade 2 and higher

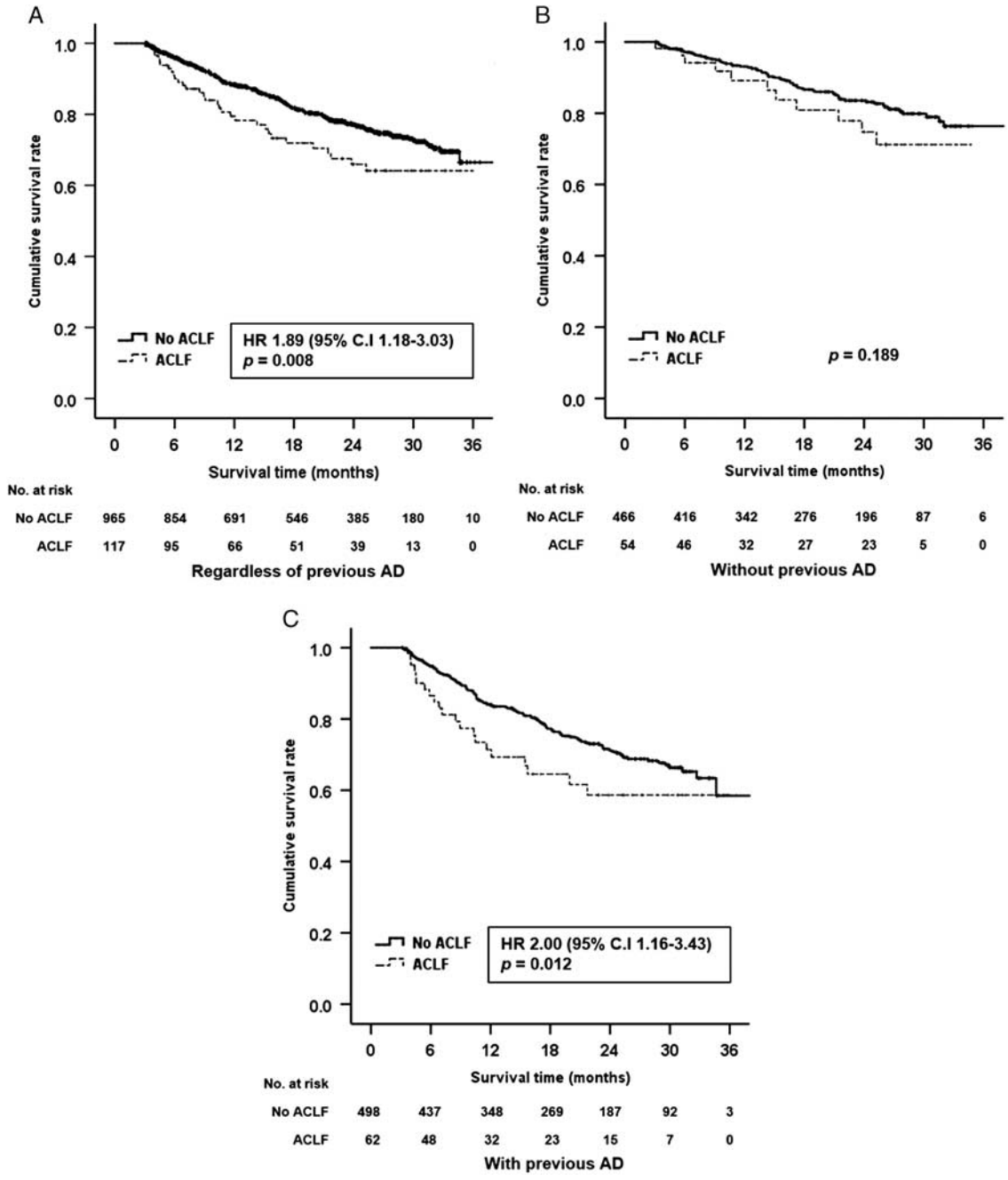

FIGURE 2. Impact of an episode of CLIF-C ACLF on long-term outcomes in patients who survived for >3 months following acute deterioration or ACLF. An ACLF episode had a negative effect on transplant-free survival in patients who survived ACLF. In Cox regression analysis, the HR for CLIF-C ACLF was 1.89 (95% CI, 1.18-3.03; $P=0.008$). A, In the subgroup of patients without a history of previous AD, no difference in transplant-free survival was observed between the patients with or without an ACLF episode. B, In the subgroup of patients with a history of previous AD, the occurrence of ACLF had a negative effect on transplant-free survival in patients who survived for >3 months following ACLF. In Cox regression analysis, the hazard ratio for CLIF-C ACLF was 2.00 (95% CI, 1.16-3.43; $P=0.012$). ACLF indicates acute-on-chronic liver failure; AD, acute decompensation; CI, confidence interval; CLIF-C, Chronic Liver Failure Consortium; HR, hazard ratio; No., number.

ACLF, respectively, as graded by the CLIF-SOFA score. The differences in the 1-year mortality rates among the groups were not significant ($P=0.219$ between patients without ACLF and grade 1 ACLF, $P=0.657$ between patients without ACLF/grade 1 ACLF and with grade 2 and higher ACLF). Similarly, in the subgroup of patients with previous AD, the 1-year mortality rates were 17.1%, 31.3%, and 33.3%, respectively. The mortality rates of those groups did not differ significantly, even with more severe organ failure (≥grade 2 by the CLIF-SOFA score) ($P=0.056$

TABLE 2. Significant Factors for Mortality in Cirrhotic Patients Who Survived ACLF

	Univariate			Multivariate		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Male	0.84	0.63-1.11	0.224			
Age (y)	1.02	1.00-1.03	0.011	1.02	1.01-1.04	<0.001
Previous AD	1.83	1.40-2.40	<0.001	1.89	1.44-2.49	<0.001
ACLF episode	1.56	1.08-2.27	0.019	0.70	0.44-1.11	0.124
Ln WBC ($\times 10^9$/L)	0.91	0.72-1.14	0.413			
Ln CRP (mg/L)	1.08	1.00-1.17	0.057			
Albumin (g/dL)	0.56	0.44-0.72	<0.001	0.69	0.53-0.89	0.005
Ln Bilirubin (mg/dL)	1.34	1.18-1.53	<0.001			
Ln prothrombin time (INR)	4.37	2.46-7.77	<0.001			
Ln creatinine (mg/dL)	1.37	1.07-1.76	0.013			
Sodium (mEq/L)	0.95	0.93-0.97	<0.001	0.97	0.95-1.00	0.016
MELD score	1.07	1.05-1.10	<0.001	1.08	1.05-1.12	<0.001

Cox regression models and hazard ratios of independent predictive factors were analyzed.

ACLF indicates acute-on-chronic liver failure; AD, acute decompensation; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; WBC, white blood cell count.

between patients without ACLF and grade 1 ACLF, $P = 0.104$ between patients without ACLF/grade 1 ACLF and with grade 2 and higher ACLF).

Significance of Previous AD in Cirrhotic Patients Who Survived >3 Months

We analyzed the difference in transplant-free survival among 1084 cirrhotic patients who survived for >3 months according to the time interval between their previous AD episode and the index acute deteriorating event (Fig. 3). The 1-year mortality rates of patients without previous AD, with previous AD >1 year before the index event, and with previous AD <1 year before the index event were 8.3% (34/410), 13.6% (34/250), and 24.4% (54/221), respectively. All between-group differences were significant (*P*-values were 0.035, 0.003, and <0.001 for comparison of the 1-year mortality between the groups of patients without previous AD, previous AD more than 1 y prior, and previous AD within 1 y, respectively). The

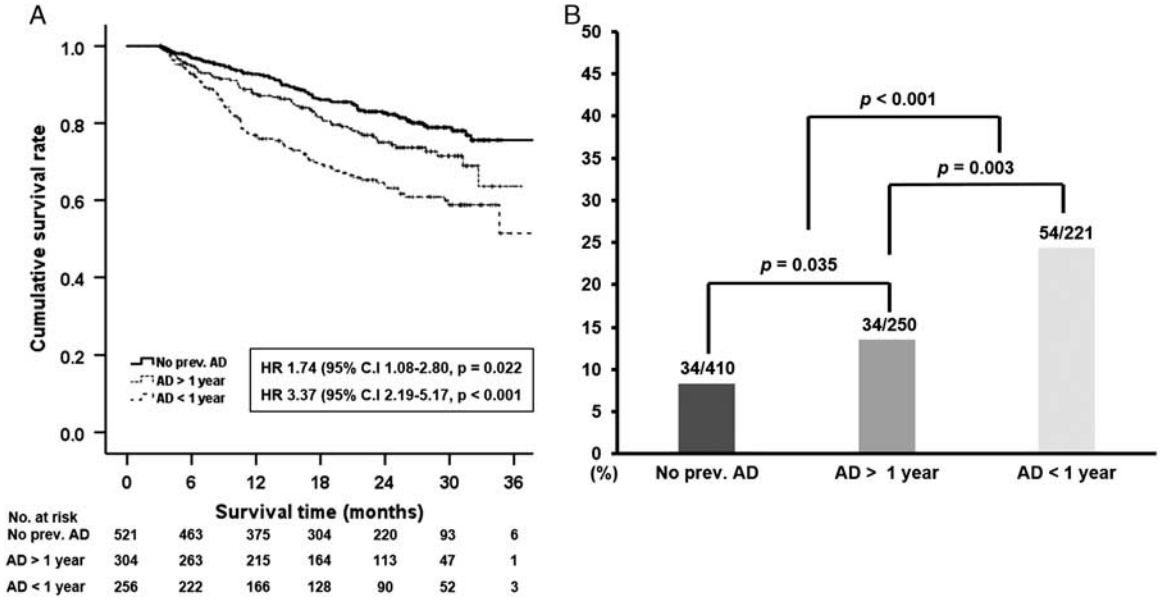

FIGURE 3. Analysis of transplant-free survival in 1084 cirrhotic patients who survived for >3 months after enrollment according to the time interval between previous and present AD episode: more than 1 year before present AD or within 1 year to present AD. A, Previous AD within 1 year of the present acute deteriorating episode was most negatively correlated with transplant-free survival ($P < 0.001$). The impact of previous AD occurring more than 1 year before the present acute deteriorating episode also negatively affected long-term outcome and did not extinguish over the follow-up period ($P = 0.022$). The HR for the 1-year transplant-free survival of previous AD more than 1 year before present acute deteriorating was 1.74, and that of the previous AD within 1 year of present acute deteriorating was 3.37. B, The 1-year mortality rates of patients without prior AD, those with previous AD more than 1 year before present acute deteriorating episode, and those with previous AD within 1 year of the present acute deteriorating episode were 8.3%, 13.6%, and 24.4%, respectively. The differences were significant for each 2-group comparison (*P*-values of 0.035, 0.003, and <0.001 for comparisons of the 1-year mortality between the group of patients without previous AD, previous AD >1 y before the present acute deteriorating episode, and previous AD within 1 y of the present acute deteriorating episode, respectively). ACLF indicates acute-on-chronic liver failure, AD, acute decompensation; CI, confidence interval; HR, hazard ratio; No., number; prev., previous.

hazard ratios for 1-year transplant-free survival of previous AD >1 year before the index acute deteriorating event and previous AD <1 year from the index event were 1.74 (95% CI, 1.08-2.80; $P=0.022$) and 3.37 (95% CI, 2.19-5.17; $P<0.001$), respectively.

Validation of the CLIF-C ACLFs and the CLIF Consortium Acute Decompensation Score (CLIF-C ADs) in the KACLiF Cohort

CLIF-C ACLFs and CLIF-C ADs are scores by which the CLIF consortium has proposed to predict mortality in patients with CLIF-C ACLF and AD patients without ACLF, respectively. These scores were calculated in our cohort patients who survived for >3 months following ACLF. The CLIF-C ACLFs in patients without previous AD and with previous AD were 93.1 ± 9.4 and 92.9 ± 9.2, respectively ($P=0.860$). Furthermore, the mean CLIF-C AD scores in the 2 groups were 54.4 ± 8.6 and 55.7 ± 8.6, respectively, with no difference observed in terms of the history of previous AD in patients who were admitted with AD but who did not develop ACLF ($P=0.435$).

Effects of Etiology on the Mortality of ACLF Patients

Among cirrhotic patients who survived for >3 months following an ACLF episode, the 6-month and 1-year mortality rates were compared according to the cirrhosis etiology. The etiologies were classified into 4 groups: viral hepatitis (VH), alcoholic liver disease (ALD), VH combined with ALD, and other. In the subgroup of patients without previous AD, the 6-month mortality rates for the VH, ALD, VH combined with ALD, and other groups were 14.3% (1/7), 5.7% (2/35), 0% (0/3), and 0% (0/3), respectively ($P=0.903$). Their 1-year mortality rates were 20% (1/5), 14.3% (4/28), 0% (0/3), and 0% (0/2), which did not differ significantly among the etiology groups ($P=0.874$). In the subgroup of patients with previous AD, the 6-month mortality rates for the VH, ALD, VH combined with ALD, and other groups were 0% (0/8), 22.5% (9/40), 0% (0/4), and 0% (0/5), respectively ($P=0.449$). The respective 1-year mortality rates were 0% (0/6), 41.6% (15/36), 25% (1/4), and 0% (0/4), and this rate was higher in the ALD group than in the VH group ($P=0.049$).

DISCUSSION

Substantial effort has been directed toward the prediction of short-term ACLF outcomes using various scoring models that calculate liver function or ACLF severity applied at different time points during the disease course[5,9–12]. In contrast, data regarding long-term ACLF prognosis are limited. Bruno et al[5] reported that the 1-, 2-, and 3-year cumulative incidences of death or liver transplantation after ACLF were 28%, 53%, and 62%, respectively. However, high long-term ACLF mortality in the aforementioned study included patients who died within a brief period due to ACLF itself. The outcome of ACLF has been suggested to depend on the hepatic reserve and the ACLF severity.[3] However, whether the severity of organ failure still affects the long-term outcome of patients who survive ACLF is not known.[13,14] ACLF is different from end-stage liver disease in that ACLF can be reversible during its course in a patient.[1] We attempted to focus on patients who survived an episode of ACLF, which might provide insight for improving the prognosis of patients who survive ACLF. Therefore, we were interested in the most significant factors in the prediction of long-term outcomes following episodes of ACLF. This can be evaluated when the effects of multiple organ failure during ACLF diminish during the course of the disease. Currently, no consensus exists regarding the definition of "ACLF recovery." Previous data show 90- and 180-day mortalities of 42% and 47% in ACLF grade 1, 74% and 79% in ACLF grade 2, and 95% and 96% in ACLF grade 3.[9] In this regard, we arbitrarily defined survival from ACLF as survival exceeding 3 months following the ACLF event. We also analyzed significant factors other than ACLF affecting long-term survival in these patients.

Consistent with previous studies, a history of previous AD was the most important predictor of mortality, even when we controlled for MELD score in our cohort after ACLF.[2] This outcome showed that a history of previous AD might affect functional hepatic reserve. This finding was quite different from the results of the CANONIC study, in which the ACLF event mortality was higher in patients without previous AD than in patients with previous AD.[1] Moreau et al[15] proposed that this can be explained by an inappropriate inflammatory response and a lack of tolerance to inflammation in patients without previous AD. Contrary to this viewpoint, we consider that decreased hepatic reserve would be the predominant factor over inappropriate inflammatory response or ACLF severity in regard to the long-term outcome of patients who have survived ACLF (Fig. 4). A high MELD score was also an independent factor in the prediction of long-term outcomes after recovery. Because we were unable to obtain the baseline patient laboratory data before enrollment (ie, before the acute deteriorating event onset), whether the elevated MELD score reflected hepatic reserve or ACLF severity was unclear. Further studies will be required to explore this topic.

Although previous AD was a significant predictor of mortality, a history of previous AD did not alter the prognosis of patients who died within 3 months after ACLF.

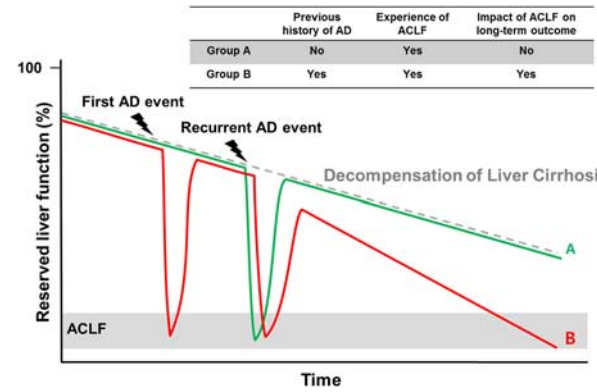

FIGURE 4. A graphical summary of the natural history according to acute decompensation and ACLF occurrences in CLD. The gray dotted line indicates the natural course of patients with decompensated liver cirrhosis. The thunderbolt signs indicate events of AD. In patients without previous AD, reserved liver function recovered after organ failure in Chronic Liver Failure Consortium ACLF after a certain recovery period of time (group A, depicted by a green solid line). However, in patients with previous AD, the occurrence of ACLF impeded reserved liver function recovery (depicted as a red solid line, group B) and affected the long-term outcome, even after a certain interval for recovery. ACLF indicates acute-on-chronic-liver failure; AD, acute decompensation.

Moreover, grade 2 and higher grades of ACLF did not affect transplant-free survival in patients who survived <3 months. Thus, we suspect that the direct effect of ACLF has a greater impact on transplant-free survival than does a history of previous AD until 3 months following the ACLF event.

Previously, Kim et al[2] reported that although a history of previous AD > 1 year before ACLF had no effect on the 90-day survival from ACLF, previous AD within 1 year of ACLF affected survival. However, the impact of previous AD > 1 year before the index deteriorating event did not extinguish in the long-term follow-up, notwithstanding the weaker impact on survival compared with that of patients with previous AD within 1 year of the index event. This is also consistent with the result of the CANONIC study, whereby the 28-, 90-, and 180-day mortality rates of patients without ACLF were 10%, 24%, and 38%, respectively, which is surprisingly progressive.[9] Therefore, we speculate that hepatic reserve does not recover in the long term but decays after an episode of AD. It is important to note that patients should be consistently educated and carefully observed so as to not be exposed to preventable etiologies of liver damage, such as uncontrolled VH or constant alcohol consumption.

The CLIF-C ACLF score, initially designed to predict 28-day mortality, has also been shown to be an effective predictor of 1-year mortality. However, it was not effective for the prediction of long-term outcomes in our cohort. This difference may be explained by the particular characteristics of our cohort, which consisted of only the patients who survived for > 3 months following ACLF. In addition, the CLIF-C Organ Failure Score and WBC, which comprise the CLIF-C ACLFs, are more closely correlated to the ACLF severity, and this effect dissipates over time.

The etiology of CLD is important in the "Predisposition-Insult-Host Response-Organ Failure" concept of ACLF. We compared transplant-free survival among groups organized by etiology, although the patient numbers in those subgroups were small. In contrast to the 6-month mortality rates, the 1-year patient survival showed differences between groups of patients with previous AD. The impact of the etiologies on survival in patients who died within 3 months after ACLF was not analyzed because etiology was not the focus of this study.

Although the transplant-free survival data were prospectively collected, our study was based on a cohort within the retrospective KACLiF study. Therefore, no additional laboratory findings were available throughout ACLF and recovery. We were also unable to obtain information about any history of active alcoholism, antiviral treatment for VH, and other factors throughout the follow-up.

We arbitrarily defined 3 months as the time for ACLF recovery; however, we were unable to directly compare differences in hepatic reserve between the time points of ACLF onset and 3 months after ACLF. Further studies are required to confirm our findings. This study may have been underpowered to analyze the effects of ACLF severity because we excluded patients who died within 3 months, and they may have had higher grades of ACLF concomitantly. Regardless, the study is unique in that the long-term transplant-free survival of ACLF was analyzed in patients who had survived the ACLF episode.

In summary, the impact of ACLF on recovery outcomes differed according to the prior history of AD. In patients with no previous AD, ACLF had no effect on long-term transplant-free survival following recovery from ACLF. However, in patients with previous AD, ACLF negatively affected long-term transplant-free survival, notably after recovery. A history of previous AD was the most significant factor in predicting long-term outcome independent of the MELD score.

In conclusion, long-term mortality after survival from ACLF depends on the history of previous AD. Among the factors studied, previous AD is the most significant, independent of the MELD score in the prediction of long-term outcome in patients who survived ACLF. The effects of organ failure severity decline over time, and this factor did not affect transplant-free survival in these patients. Preventing the first AD episode may improve long-term transplant-free survival in patients with liver cirrhosis.

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