

# Clinical Features of Hepatitis C Virus-Related Acute-On-Chronic Liver Failure in a Korean Population

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## Research Article

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# Abstract

## Background

Acute-on-chronic liver failure (ACLF) is a widely recognized concept in which acute decompensation (AD) in patients with cirrhosis results in organ failures and high short-term mortality. However, few studies reflecting the various etiologies of cirrhosis are available. We aimed to investigate the clinical features of patients with hepatitis C virus (HCV)-related ACLF.

## Methods

Between January 2005 and December 2018, 109 HCV-related cirrhosis patients who were hospitalized for AD (ascites, hepatic encephalopathy, gastrointestinal hemorrhage, and/or bacterial infection) were enrolled for ACLF defined by European Association for the Study of the Liver (EASL).

## Results

ACLF developed in 35 patients (32.1%) on admission. Eight patients had ACLF grade 1, eight had ACLF grade 2, and 19 had ACLF grade 3. The 28-day and 90-day mortality rates were very low (2.7% and 5.4%, respectively) in patients without ACLF and very high (60.0% and 74.3%, respectively) in those with ACLF. In patients with HCV-related ACLF, the prevalence of liver failure was very low (17.1%), whereas that of kidney failure was very high (71.4%) compared to previous studies on hepatitis B virus-related ACLF and alcohol-related ACLF. Compared with all other prognostic scores, Chronic liver failure Consortium Organ Failure score most accurately predicted 90-day mortality, with an area under the receiver operator characteristic of 0.921.

## Conclusions

HCV-related ACLF has unique clinical characteristics that are distinct from hepatitis B virus-related and alcohol-related ACLF. ACLF defined by EASL can be useful in predicting short-term mortality in HCV-related cirrhosis.

## Background

Acute-on-chronic liver failure (ACLF) is a recently increasingly recognized syndrome in which acute decompensation (AD) leads to rapid liver and extra hepatic organ failure associated with high short-term mortality in patients with chronic liver disease [1–4]. Patients with ACLF have 28-day mortality rates of approximately 30% and 90-day mortality rates in exceeding 50% [5–7].

However, there is no diagnostic criteria for ACLF globally. Recently, two definitions of ACLF proposed by the Asian Pacific Association for the Study of the Liver (APASL) and the European Association for the Study of the Liver (EASL) are currently widely accepted. APASL-ACLF was defined first in 2009 as a rapid deterioration manifesting as jaundice (serum bilirubin  $\geq 5$  mg/dL) and coagulopathy (prolonged international normalized ratio (INR)  $\geq 1.5$ ) complicated by clinical ascites and/or hepatic encephalopathy (HE) in patients with previously known or unknown chronic liver disease [6]. In contrast, the EASL-ACLF, from the CANONIC study, was defined as AD (HE, gastrointestinal (GI) hemorrhage, ascites, or bacterial infection) in pre-existing cirrhosis patients followed by the development of multi-system organ failures [5].

Another important problem beyond the ongoing controversies surrounding diverse ACLF definitions is that the data that have been studied do not reflect the various causes of cirrhosis. The definition of APASL-ACLF was derived from a cohort consisting of patients predominantly infected by hepatitis B virus (HBV), whereas in the EASL-ACLF cohort, nearly 60% of patients had alcoholic liver disease. Subsequently, the Chinese Group on the Study of Severe Hepatitis B (COSSH) developed a new definition for HBV-related ACLF [8]. The Korean Acute-on-Chronic Liver Failure study cohort was proposed in cirrhosis patients from Korea, but this study had a population rate of alcoholic liver disease in excess of 60% [7, 9]. Lee et al. recently investigated the ability of chronic liver failure sequential organ failure assessment (CLIF-SOFA) to predict short-term mortality in patients with alcohol-related ACLF [10].

However, to date, no studies have included patients with hepatitis C virus (HCV)-related ACLF. Therefore, we sought to identify the clinical features of patients of HCV-related ACLF in Korea, an HBV endemic area.

## Patients And Methods

### Study population

This retrospective cohort study included 1743 patients with HCV infection who visited the Gyeongsang National University Changwon Hospital and Gyeongsang National University Hospital from January 2005 to December 2018. The exclusion criteria were as follows: (1) a follow-up period of less than 6 months (n = 273); (2) presence of hepatocellular carcinoma (n = 143); (3) presence of extrahepatic malignancy or severe extrahepatic disease (n = 37); (4) HBV co-infection (n = 53); (5) human immunodeficiency virus infection co-infection (n = 5); and (6) acute HCV infection (n = 10). Among the remaining 1222 patients with chronic hepatitis C, 1008 without cirrhosis and 214 with cirrhosis were initially analyzed for ACLF using the APASL criteria (total bilirubin  $\geq 5$  mg/dL and INR  $\geq 1.5$ ), applied to patients with chronic liver disease with or without cirrhosis. To apply the EASL-ACLF, after excluding 1008 patients without cirrhosis and 105 patients without AD events as defined by the acute development of overt ascites, HE, GI hemorrhage, and bacterial infection, 109 patients with cirrhosis who developed AD were finally analyzed (Fig. 1). The study was approved by the Institutional Review Boards of Gyeongsang National University Changwon Hospital and Gyeongsang National University Hospital. The need for informed consent was

waived due to the retrospective design of this study, as determined by the Institutional Review Boards of Gyeongsang National University Changwon Hospital and Gyeongsang National University Hospital.

## Data collection and definition

We collected data from the medical charts, including patient demographics, clinical and laboratory data on admission, types of AD events and organ failures, potential precipitating factors of AD and ACLF, and development of ACLF. Potential precipitating factors included bacterial infection, GI hemorrhage, active alcoholism, large volume paracentesis without albumin, transjugular intrahepatic portosystemic shunting, major surgery, hepatitis (including reactivation of viral hepatitis and toxic liver injury), and alcoholic hepatitis. Active alcoholism was defined as > 14 drinks per week in women and > 21 drinks per week in men within the last three months [5]. AD events were defined as acute onset of HE, ascites, GI hemorrhage, bacterial infection, or any combination of these. Organ failure was defined according to a modified CLIF Consortium Organ Failure score (CLIF-C OFs) [11], which is a simplified modification of the CLIF-SOFA score and entails the following: liver failure, defined as total bilirubin level of  $\geq 12$  mg/dL; kidney failure, defined as serum creatinine level of  $\geq 2.0$  mg/dL and/or requiring renal replacement therapy; cerebral failure, defined as grade III or IV HE based on West Haven criteria; coagulation failure, defined as INR > 2.5; circulation failure, defined as treatment with vasoconstrictors to maintain the arterial blood pressure or inotropes to improve cardiac output; and respiratory failure, defined as  $\text{PaO}_2/\text{FiO}_2 \leq 200$  or  $\text{SpO}_2/\text{FiO}_2 \leq 214$ .

According to the EASL-ACLF criteria, the severity of ACLF was graded into ACLF grade 1 (ACLF-1), ACLF grade 2 (ACLF-2), or ACLF grade 3 (ACLF-3) according to the number of organ failures. ACLF-1 was defined by the presence of a single kidney failure or any other organ failure when in combination with either kidney dysfunction (serum creatinine ranging 1.5 to 1.9 mg/dL) or grade I or II HE. ACLF-2 or 3 was defined by the presence of 2 or  $\geq 3$  organ failures, respectively. We assessed the ACLF and ACLF grades, as defined above, by investigating for any association of organ failure at admission.

## Prognostic score

The performance of CLIF-C OFs in evaluating prognosis was comparable to that of the CLIF-SOFA score [11]. To predict short-term mortality in cirrhosis patients with AD, we compared the performance of CLIF-C OFs with that of Child-Pugh-Turcotte (CTP) scores, model for end-stage liver disease (MELD) score and MELD-sodium (MELD-Na) score. In addition, the CLIF-C ACLF score (CLIF-C ACLFs) was used to predict short-term mortality in ACLF patients [11], and the CLIF-C AD score (CLIF-C ADs) was used in AD patients without ACLF [12].

## Statistical analysis

Fisher's exact and Pearson's chi-square tests to analyze the qualitative data and the Mann-Whitney U test to analyze the quantitative data were performed to assess the association between patient characteristics and ACLF at admission. Survival rates for the development of 90-day survival were estimated by the Kaplan-Meier method and compared using the log-rank test. The accuracy of the CLIF-

OFs, CTP score, MELD score, and MELD-Na score in predicting survival was assessed by area under the receiver operating characteristic (AUROC) curve. A *P*-value < 0.05 was considered statistically significant for all analyses. All statistical operations were performed using PASW Statistics, version 18 (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Patients with non-cirrhotic chronic hepatitis C did not exhibit ACLF as defined by APASL (total bilirubin  $\geq$  5 mg/dL and INR  $\geq$  1.5). Thus, the EASL-ACLF criteria were chosen to define ACLF in this study. The baseline characteristics of 109 patients with HCV-related cirrhosis are shown in Table 1. Of cirrhosis patients with AD, ACLF developed in 35 patients (32.1%) on admission. Eight patients (7.3%) had ACLF-1, eight (7.3%) had ACLF-2, and 19 (17.4%) had ACLF-3. There was no significant difference in age, sex, HCV genotype, and sustained virologic response rate between patients with and without ACLF. Overt ascites was the most common type of AD, followed by bacterial infection, GI hemorrhage, and HE. GI hemorrhage, bacterial infection, and HE were more frequent in patients with ACLF than in patients without ACLF. History of AD was reported in 35 (32.1%) patients. Patients with ACLF more frequently had prior AD events.

Table 1

Baseline characteristics of patients with HCV-related cirrhosis at admission according to ACLF

Characteristics	Overall (n = 109)	No ACLF (n = 74)	ACLF (n = 35)	<i>P</i>
Age, year	62.0 (53.0–71.5)	63.0 (53.0–72.3)	61.0 (51.0–70.0)	0.638
Male sex	65 (59.6%)	43 (58.1%)	22 (62.9%)	0.680
HCV genotype				0.594
1	50 (45.9%)	32 (43.2%)	18 (51.4%)	
2	45 (41.3%)	33 (44.6%)	12 (34.3%)	
3	14 (12.8%)	9 (12.2%)	5 (14.3%)	
SVR at enrollment	12 (11.0%)	7 (9.5%)	5 (14.3%)	0.517
Causes of hospitalization				
Ascites	50 (45.9%)	36 (48.6%)	14 (40.0%)	0.419
HE	24 (22.0%)	7 (9.5%)	17 (48.6%)	< 0.001
GI hemorrhage	36 (33.0%)	30 (40.5%)	6 (17.1%)	0.017
Bacterial infection	37 (33.9%)	17 (23.0%)	20 (57.1%)	0.001
Precipitating events				
Bacterial infection	37 (33.9%)	17 (23.0%)	20 (57.1%)	0.001
GI hemorrhage	36 (33.0%)	30 (40.5%)	6 (17.1%)	0.017
Active alcoholism	11 (10.1%)	7 (9.5%)	4 (11.4%)	0.743
Other precipitating events	5 (4.6%)	1 (1.4%)	4 (11.4%)	0.036
No precipitating event	31 (28.4%)	24 (32.4%)	7 (20.0%)	0.256
More than one precipitating event	9 (8.3%)	4 (5.4%)	5 (14.3%)	0.143
Organ failure				
Liver	7 (6.4%)	1 (1.4%)	6 (17.1%)	0.004
Abbreviation: ACLF, acute on chronic liver failure; SVR, sustained virologic response; HE, Hepatic encephalopathy; GI, Gastrointestinal; AD, acute decompensation.				
<i>P</i> : Mann-Whitney U-test and Chi-squared test. Data are presented as the median (interquartile range) for continuous data and percentages for categorical data.				

Characteristics	Overall (n = 109)	No ACLF (n = 74)	ACLF (n = 35)	<i>P</i>
Kidney	25 (22.9%)	0	25 (71.4%)	< 0.001
Cerebral	26 (23.9%)	7 (9.5%)	19 (54.3%)	< 0.001
Coagulation	12 (11.0%)	0	12 (34.3%)	< 0.001
Circulation	19 (17.4%)	0	19 (54.3%)	< 0.001
Respiration	17 (15.6%)	1 (1.4%)	16 (45.7%)	< 0.001
Kidney dysfunction	8 (7.3%)	4 (5.4%)	4 (11.4%)	0.267
Time from first previous AD				< 0.001
No previous AD	74 (67.9%)	59 (79.7%)	15 (42.9%)	
Less than 12 months	14 (12.8%)	7 (9.5%)	7 (20.0%)	
More than 12 months	21 (19.3%)	8 (10.8%)	13 (37.1%)	
Abbreviation:ACLF, acute on chronic liver failure; SVR, sustained virologic response; HE, Hepatic encephalopathy; GI, Gastrointestinal; AD, acute decompensation.				
<i>P</i> . Mann-Whitney U-test and Chi-squared test. Data are presented as the median (interquartile range) for continuous data and percentages for categorical data.				

On admission, patients with ACLF had higher median white blood cell, total bilirubin, creatinine, and INR levels but lower median albumin and sodium levels than those without ACLF (Table 2). Prognostic scores revealed that patients with ACLF had higher CTP scores, MELD scores, MELD-Na scores, and CLIF-OFs than those without ACLF.

Table 2  
Prognostic scores and laboratory data at admission

Characteristics	Overall (n = 109)	No ACLF (n = 74)	ACLF (n = 35)	P
Prognostic scores				
CTP	9.0 (7.0–11.0)	8.0 (7.0–10.0)	10.0 (8.0–12.0)	< 0.001
MELD	14.0 (9.5–21.5)	11.0 (9.0–15.3)	26.0 (20.0–31.0)	< 0.001
MELD-Na	18.0 (12.0–25.0)	14.5 (11.0–18.3)	28.0 (22.0–33.0)	< 0.001
CLIF-C OFs	6.0 (6.0-8.5)	6.0 (6.0–6.0)	9.0 (12.0–14.0)	< 0.001
CLIF-C ADs		48.0 (44.0–54.0)		
CLIF-C ACLFs			54.0 (46.0–61.0)	
Laboratory data				
WBC, $10 \times 10^9/L$	6.3 (4.3–9.8)	5.7 (4.2–8.0)	9.4 (4.9–12.5)	0.005
Hemoglobin, g/dL	10.7 (8.8–12.3)	11.2 (8.8–12.7)	10.1 (8.6–11.8)	0.150
Platelet, $\times 10^9/L$	107.0 (67.0–136.5)	109.0 (70.0–139.5)	100.0 (54.0–127.0)	0.270
Bilirubin, mg/dL	1.6 (0.8–3.1)	1.3 (0.6–2.9)	2.4 (1.3–5.0)	0.001
AST, U/L	59.0 (38.0–96.0)	57.5 (37.8–84.5)	60.0 (38.0- 161.0)	0.345
ALT, U/L	35.0 (20.0–62.0)	35.0 (20.0–53.5)	28.0 (38.0–161.0)	0.820
Albumin, g/dL	2.7 (2.5–3.1)	2.9 (2.6–3.1)	2.5 (2.1–2.8)	< 0.001
Creatinine, mg/dL	0.90 (0.69–1.64)	0.76 (0.62–0.90)	2.33 (1.69–2.96)	< 0.001
Sodium, mmol/L	136.0 (132.0–139.4)	136.3 (133.4- 139.3)	133.2 (127.5–140.1)	0.045
PT-INR	1.42 (1.21–1.73)	1.31 (1.17–1.56)	1.81 (1.39–2.61)	< 0.001
<p>Abbreviation: ACLF, acute on chronic liver failure; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease-sodium; CLIF-C OFs, Chronic Liver Failure-Consortium Organ Failure Score; CLIP-C ADs, CLIF Consortium Acute Decompensation score; CLIP-C ACLFs, CLIF-Consortium scores for ACLF; WBC, white blood cell; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; PT-INR, prothrombin time- international normalized ratio.</p> <p>P: Mann-Whitney U-test and Chi-squared test.</p> <p>Data are presented as the median (interquartile range) for continuous data and percentages for categorical data.</p>				

## Organ failures and precipitating events

Patients with ACLF more frequently had bacterial infection, GI hemorrhage, and a composite of other precipitating events than those without ACLF. No precipitating event was found in 28.4% of patients

(Table 1). Skin infection (23.5%) was the most common type of bacterial infection, followed by pneumonia (17.6%), colitis (17.6%), spontaneous bacterial peritonitis (11.8%), urinary tract infection (11.8%), and unproved (5.9%) (Supplementary Table 1). The most common type of organ failure in patients with ACLF involved the kidney (71.4%), followed by the brain (54.3%), circulation (54.3%), the lungs (45.7%), coagulation (34.3%), and the liver (17.1%).

## Short-term mortality and prognostic scores

Kaplan-Meier curves of the probability of survival revealed that patients with ACLF had poorer outcomes than those with AD (Fig. 2A). Mortality at 28 days, 90 days, and 1 year for patients without ACLF was 2.7%, 5.4%, and 9.5%, respectively while mortality at 28 days, 90 days, and 1 year for patients with ACLF was 60.0%, 74.3%, and 80.0%, respectively (Fig. 2B). Mortality at 28 days and 90 days was 2.7% and 5.4% for patients without ACLF, 0% and 37.5% for those with ACLF-1, 75.0% and 87.5% for those with ACLF-2, and 78.9% and 89.5% for those with ACLF-3, respectively (Supplementary Fig. 1). In the survival curve according to prior AD, there was a significant difference in the survival rates of patients with or without ACLF, but there was no significant difference in the survival rates of patients according to prior AD (Supplementary Fig. 2). Multiple organ failure without septic shock or hypovolemic shock was the most common cause of death at 90 days (53.3%), followed by septic shock (20.0%) and hypovolemic shock (16.7%) (Supplementary Table 2).

Median CLIF-C ADs in patients without ACLF ( $n = 74$ ) and CLIF-C ACLFs in patients with ACLF ( $n = 35$ ) were 48.0 and 54.0, respectively. A strong stepwise association was observed between CLIF-C OFs and ACLF grades in cirrhosis patients with AD (Supplementary Fig. 3). Median CLIF-C OFs were 6.0, 7.5, 10.0, and 13.0 in patients without ACLF, ACLF-1, ACLF-2, and ACLF-3, respectively. All prognostic scores, including CTP score, MELD score, MELD-Na score, and CLIF-C OFs, were significantly higher in patients with ACLF than in those without ACLF (Table 2). In all patients ( $n = 109$ ), median CLIF-C OFs were significantly higher in patients who died within 90 days than in those who did not die (12.0 vs. 6.0,  $P < 0.001$ ) (Supplementary Fig. 4A). In patients without ACLF, there was no significant difference in median CLIF-ADs between patients who did and did not die (49.5 vs. 48.0,  $P = 0.881$ ) (Supplementary Fig. 4B). In patients with ACLF, there was no significant difference in median CLIF-ACLFs between patients who did and did not die (54.0 vs. 47.0,  $P = 0.342$ ). Among all prognostic parameters in all patients, CLIF-C OFs revealed the highest AUROC (0.921, 95% confidence interval [CI]: 0.855–0.986) for predicting 90-day mortality (Fig. 3).

Meanwhile, ACLF, as defined by APASL, developed in ten patients (9.2%) at admission in 109 patients with AD and cirrhosis. Mortality at 28 days, 90 days, and 1 year for patients without APASL-ACLF was 17.2%, 21.2%, and 26.3%, respectively, while mortality at 28 days, 90 days, and 1 year for patients with APASL-ACLF was 60.0%, 90.0%, and 90.0%, respectively (Supplementary Fig. 5).

## Discussion

In this study of 109 patients with HCV-related cirrhosis who were hospitalized for AD (ascites, HE, GI hemorrhage, and/or bacterial infection), 28-day and 90-day mortalities were higher in patients with ACLF at admission than in those without ACLF (60.0% and 74.3% vs. 2.7% and 5.4%, respectively). In addition, the CLIF-C OFs were the most accurate in predicting 90-day mortality for HCV-related cirrhosis patients who had AD compared with the CTP score, MELD score, and MELD-Na score.

Among the various definitions of ACLF, no studies have been conducted in a cohort consisting only of patients with HCV-related chronic liver disease. In our chronic hepatitis C cohort of 1222 patients, no patient met the definition of APASL-ACLF (total bilirubin  $\geq 5$  mg/dL and INR  $\geq 1.5$ ) in patients without cirrhosis. There are very few episodes of acute flare-ups in chronic hepatitis C patients, even in immunocompromised patients.[13] Therefore, non-cirrhotic HCV-ACLF rarely occurs in chronic hepatitis C without cirrhosis, unlike in non-cirrhotic HBV-ACLF [8, 14, 15]. This suggests that the APASL-ACLF criteria or COSSH criteria cannot be applied to patients with non-cirrhotic chronic hepatitis C. Among 109 HCV-related cirrhosis patients, eight had EASL-ACLF and APASL-ACLF, 27 had EASL-ACLF alone, and two had APASL-ACLF alone. Therefore, the EASL-ACLF criteria detected more ACLF patients even in the setting of chronic hepatitis with cirrhosis. In a previous study using data from the Veterans Health Administration, the incidence of ACLF for patients with hepatitis C was higher in EASL-ACLF criteria than in APASL-ACLF [16]. In our study, patients with EASL-ACLF on admission had a significantly higher 90-day mortality rate than patients without EASL-ACLF. In particular, patients with ACLF-2 and ACLF-3 on admission had extremely high 90-day mortality (87.5% and 89.5%, respectively), while patients with no ACLF had very low 90-day mortality (5.4%). These suggest that EASL-ACLF is a very useful tool for predicting the prognosis in HCV-related cirrhosis patients who were hospitalized for acute deterioration. To our knowledge, our study is the first study on HCV-related ACLF that does not contain ACLF of other etiologies.

HCV-related ACLF showed distinctive characteristics that distinguished ACLF from other causes. The 90-day mortality for patients ACLF was highest in our study, composed of HCV-related ACLF (74.3%), compared with the COSSH study (HBV-related ACLF, 69.7%),[8] the Korean study (alcohol-related ACLF, 67.2%) [10], and the CANONIC study, composed of various etiologies (51.2%) [5]. Comparing the prevalence of organ failure, liver failure in HCV-related ACLF was very low (17.1%) compared to HBV-related ACLF (93.7%) and the CANONIC study (43.6%) [5, 8]. On the other hand, the prevalence of kidney failure in HCV-related ACLF was very high (71.4%) compared to that of HBV-related ACLF (14.0%) and the CANONIC study (55.8%). Therefore, ACLF in HCV-related cirrhosis may be associated with kidney failure rather than liver failure, which is thought to be associated with high short-term mortality. These suggest that the mechanism for HCV-ACLF probably reflects an extrahepatic insult, such as bacterial infection and GI hemorrhage, while the mechanism for HBV-ACLF probably reflects a hepatic insult, such as HBV flare. In a recent large-scale retrospective cohort study in the United States, patients with hepatitis C had the lowest ACLF incidence rate but had the highest short-term mortality compared with patients with HBV-related ACLF and alcohol-related ACLF [16].

CLIF-C OFs displayed the best prognostic ability for cirrhosis patients with AD (AUROC = 0.921, 95% CI 0.855–0.986) compared to the CTP score, MELD score, and MELD-Na score. CTP, MELD, and MELD-Na scores are based only on liver failure (bilirubin), kidney failure (creatinine), coagulation failure (INR), and cerebral failure (HE), whereas CLIF-C OFs additionally reflect coagulation and respiratory failure to predict the prognosis more effectively. The CLIF-SOFA score is a widely used tool in predicting short-term mortality in ACLF and AD patients and is superior to MELD score in predicting prognosis [10, 14, 17, 18]. Our study showed that short-term mortality can be effectively predicted using CLIF-C OFs, a simplified modification of the CLIF-SOFA score.

This study had some limitations. First, this was a retrospective study with a relatively small sample size. We were unable to accurately access HE grade 1 and 2 for measuring CLIF-C OFs through a retrospective chart review. Second, we excluded patients who were lost to follow-up within six months after transferring to other hospitals for liver transplantation because our institute cannot perform liver transplantation. Third, most HCV-infected patients in this study did not receive antiviral therapy because they were enrolled before the direct acting agent era or consisted of severe decompensated cirrhosis. Despite these limitations, the strength of our study is that it is the first study to identify the clinical features of patients HCV-related ACLF, especially in Korea, an HBV endemic area.

## **Conclusion**

Applying the EASL-ACLF definition to patients with HCV-related cirrhosis can be useful in predicting short-term mortality, consistent with previous studies conducted on the other etiologies. Additionally, HCV-related ACLF has unique clinical features that are distinct from HBV-related or alcohol-related ACLF.

## **Declarations**

### **Ethics approval and consent to participate**

The project was approved by the Institutional Review Board of Gyeongsang National University Changwon Hospital (IRB No. 2019-08-030) and Gyeongsang National University Hospital (IRB No. 2014-04-028). Informed consent was waived given that all of the personal data obtained were anonymized before analysis, as determined by the Institutional Review Boards of Gyeongsang National University Changwon Hospital and Gyeongsang National University Hospital. All methods in this study were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration.

### **Consent for publication**

Not applicable.

### **Availability of data and material**

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and confidentiality reasons but are available from the corresponding author on reasonable request under the Gyeongsang National University Changwon Hospital and Gyeongsang National University Hospital Ethics Committee's approval. The data that support the findings of this study are available on request to the correspondence author. (Sang Soo Lee, Email:3939lee@naver.com)

### **Competing interests**

The authors declare that they have no competing interests.

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**Authors' Contributions:** Conception and design: JWC, JKC, and SSL

Data collection: JHK, HJ, HeeJK, RRC, JML, and HyunJK.

Data analysis and interpretation: JWC, JKC, and SSL

Manuscript writing: JWC and SSL

Final approval of manuscript: All authors.

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## Supplementary Materials

Supplementary Figure 1. Mortality at 28 days and 90 days according to grades of ACLF.

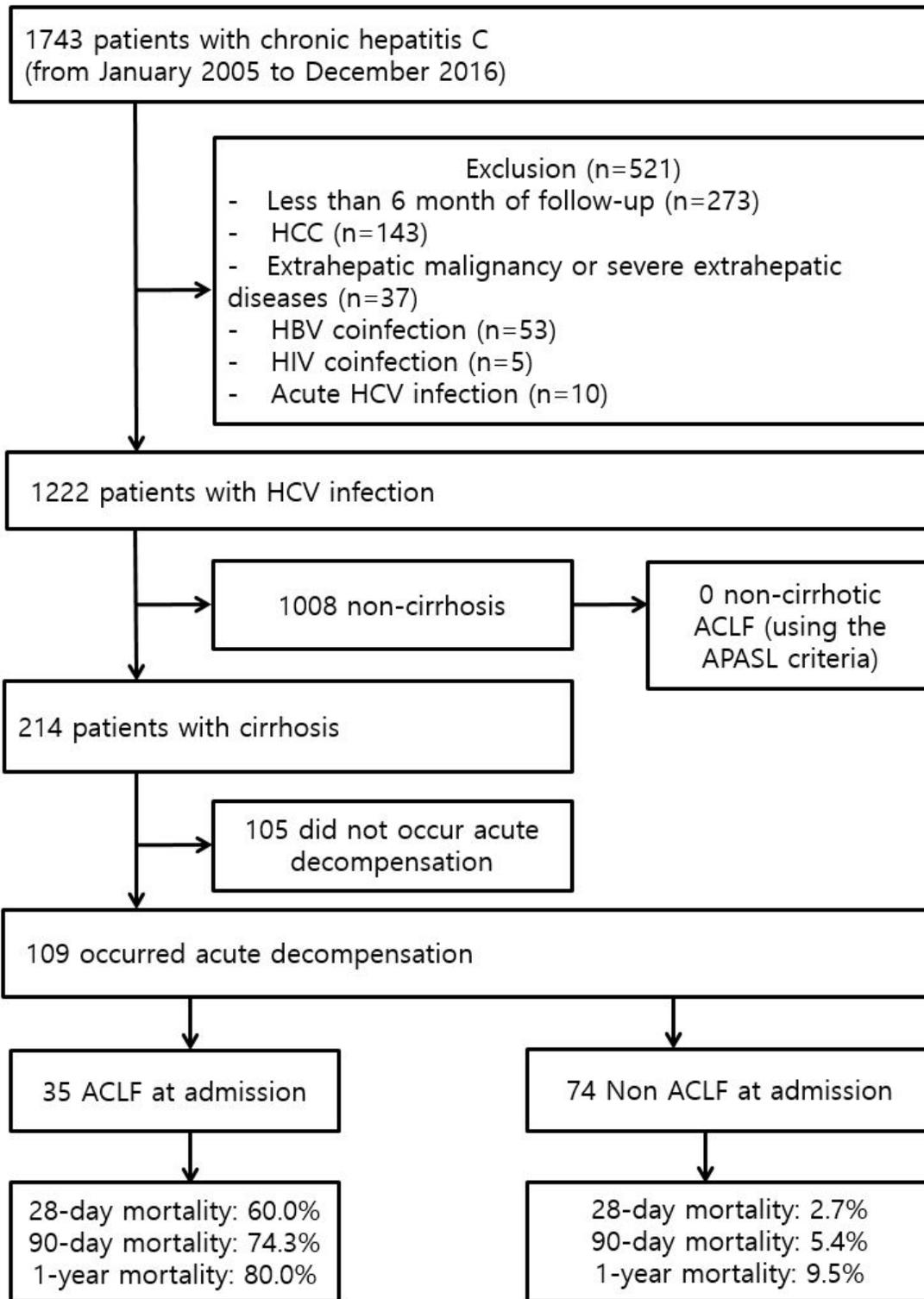
Supplementary Figure 2. Survival curves in patients with or without ACLF according to prior acute decompensation.

Supplementary Figure 3. CLIF-C OF score according to grades of ACLF.

Supplementary Figure 4. Prognostic scores according to death. (A) CLIF-C OF scores in entire patients (n=109). (B) CLIF-C AD score in patients without ACLF (n=74). (C) CLIF-C ACLF score in patients with ACLF (n=35).

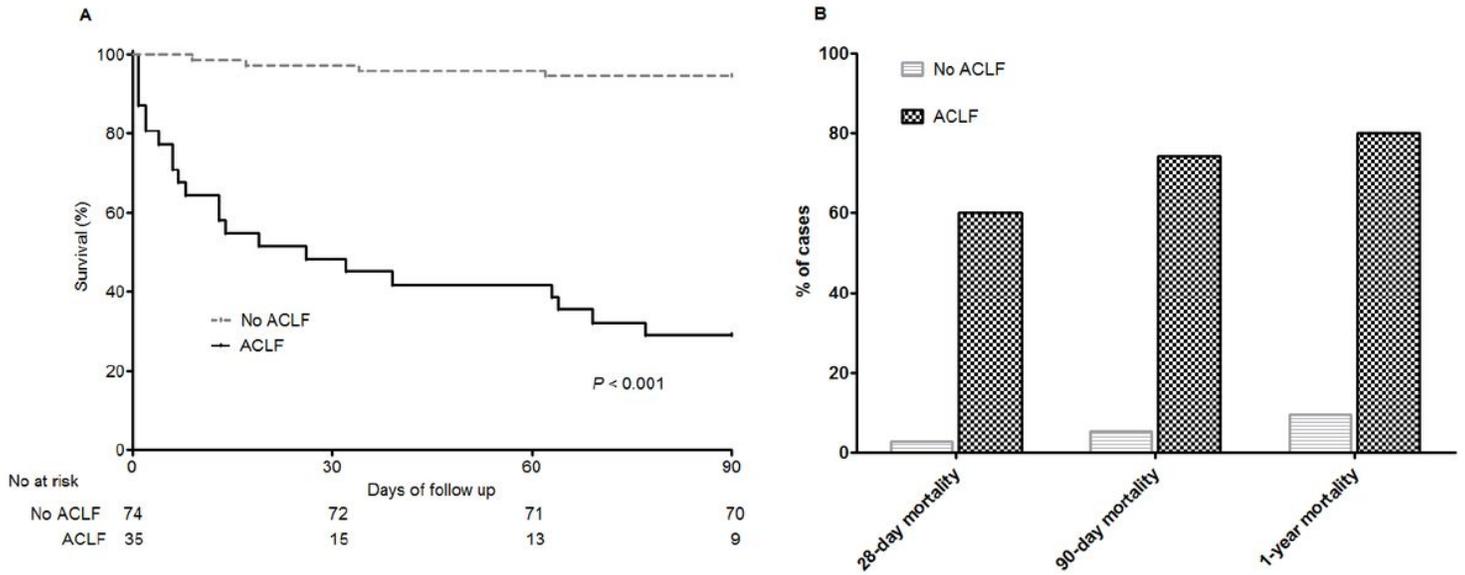
Supplementary Figure 5. Mortality at 28 days and 90 days of patients with or without AARC-ACLF.

## Figures



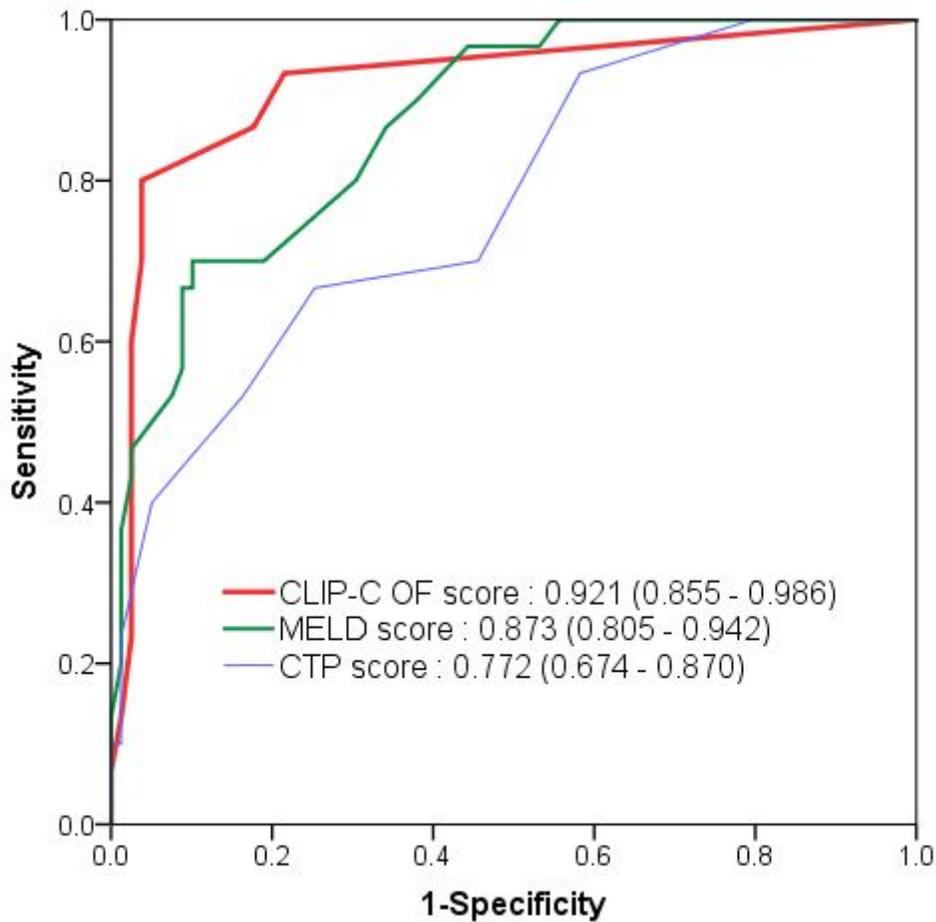
**Figure 1**

Flow sheet



**Figure 2**

Prognosis according to ACLF. (A) Kaplan-Meier curves of the probability of survival within 28 days. (B) Mortality at 28 days, 90 days, and 1 year of patients without or with ACLF.



**Figure 3**

Receiver operating characteristic curves of the CLIF-C OF score and three prognostic scoring systems in predicting 90-day mortality in HCV-related cirrhosis with acute decompensation (n=109).

## Supplementary Files

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