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RESEARCH ARTICLE

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Aetiology of chronic liver disease is a valuable factor for stratifying adverse outcomes of acute decompensation: prospective observational study

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ABSTRACT

Background/Aims: Acute decompensation (AD) is defined as the development of complications related to portal hypertension and liver dysfunction that affect the progression of chronic liver disease (CLD) or liver cirrhosis (LC). Variations exist in patient demographics and prognostic outcomes of AD based on the aetiology of CLD, encompassing LC. However, limited research has been conducted to analyse these discrepancies across aetiologies.

Methods: The prospective Korean Acute-on-Chronic Liver Failure (KACLiF) cohort consisted of 1,501 patients who were hospitalized with AD of CLD from July 2015 to August 2018. In this study, we assess the clinical attributes and prognostic implications of AD with CLD/LC stratified by the aetiology.

Results: Among 1,501 patients, the mean age was 54.7 years old and 1,118 patients (74.5%) were men. The common events of AD were GI bleeding (35.3%) and jaundice (35.0%). There was a median follow-up of 8.0 months (1.0–16.0 months). The most common aetiology of CLD was alcohol ($n=1021$), followed by viral hepatitis ($n=206$), viral hepatitis with alcohol-related ($n=129$), cryptogenic ($n=108$) and autoimmune ($n=37$). Viral hepatitis with alcohol-related CLD showed a poor liver function profile and a high frequency of acute-on-chronic liver failure (ACLF) [22.1% vs. 19.6% (alcohol CLD), 8.1% (viral CLD), 5.6% (autoimmune related CLD and 16.0% (cryptogenic CLD)] with worse adverse outcomes (mortality or liver transplantation) than other aetiologies. The difference in aetiology was a significant factor for 28-day adverse outcomes in multivariate analysis even in a high MELD score (≥15), which indicated poor baseline liver function and prognosis ($p<0.001$).

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Conclusion: The aetiology of CLD constitutes a pivotal determinant influencing both short- and long-term adverse outcomes of AD in CLD, even among individuals presenting with elevated MELD scores. Notably, patients afflicted with viral hepatitis should exercise caution even in the consumption of modest quantities of alcohol that induced the exacerbations in the adverse outcomes associated with AD.

Abbreviations: AD: acute decompensation; LT: liver transplantation; LC: liver cirrhosis; CLD: chronic liver disease; ACLF: acute-on-chronic liver failure; MELD: Model for End-Stage Liver Disease; HCV: hepatitis C virus; HBV: hepatitis B virus; SIRS: systemic inflammatory response syndrome; CTP: Child-Turcotte-Pugh score; CLIF-SOFA: score: Chronic Liver Failure Sequential Organ Failure Assessment; CVD: cerebrovascular disease; DM: diabetes mellitus; HTN: hypertension; HCC: hepatocellular carcinoma

Introduction

Acute decompensation (AD) is a widely accepted status defined as the acute development of one or more major complications, such as ascites, encephalopathy, gastrointestinal (GI) bleeding and bacterial infection, in patients with chronic liver disease (CLD), especially liver cirrhosis (LC) [1, 2]. AD is the main cause of hospitalization among patients with LC [1–3]. AD develops in most LC patients in the absence of any other significant feature, while in approximately 30% patients, it is associated with organ failure(s) (i.e. worsening of liver function and/or kidney failure and/or failure of other organs) [1, 4]. For instance, over a span of 10 years, approximately 60% of patients diagnosed with cirrhosis may develop ascites, while variceal bleeding escalates the annual incidence by 8–12% among cirrhotic individuals [5]. Depending on the severity of the AD event and the degree of underlying liver function impairment, multi-organ dysfunction may ensue [2, 4]. Acute-on-chronic liver failure (ACLF) represents an advanced manifestation of acutely decompensated cirrhosis distinguished by the presence of multi-organ dysfunction and an elevated risk of short-term mortality [4]. Patients with ACLF are at high risk for short-term death, regardless of their CLD aetiologies [2, 6–8]. Interestingly, there is a significant difference in the distribution of aetiologies of CLD in Western countries and Asian countries. In a recent systemic review that involved the analysis of 520 studies, the prevalence of HBV infection exhibited greater incidence rates in Africa and Asia (8%–61%) compared to Europe, the Americas and Oceania (3%–14%). Conversely, the prevalence of HCV infection demonstrated significant heterogeneity across countries and regions, with rates ranging from 12% to 83%. However, the global burden of hepatitis B virus and hepatitis C virus-associated cirrhosis is declining, while the burden of cirrhosis attributable to alcohol and nonalcoholic fatty liver disease (NAFLD) is rapidly escalating [9]. In Korea, the predominant aetiology, particularly associated with acute decompensation (AD) in 21 academic hospitals, was alcohol-related chronic liver disease (CLD), accounting for 63.1% (928 out of 1,470 cases) over the course of 1 year [6]. Regardless of the aetiology of CLD with AD, AD and its worst form, acute-on-chronic liver failure (ACLF), are undoubtedly highly correlated with adverse outcomes such as mortality and liver transplantation (LT) in CLD, including LC [4]. It is thought that there are differences in patient characteristics and the prognosis of AD development according to the aetiologies of CLD, including LC, but there has been no study to investigate this to date. Additionally, it is not yet known which aetiology of CLD has the worst prognosis for these patients. Therefore, we aimed to investigate the differences in characteristics and short-term and long-term adverse outcomes among CLD patients with AD according to each aetiology in the prospective Korean Acute-on-Chronic Liver Failure (KACLiF) cohort. In addition, we investigated the risk factors for adverse outcomes according to each aetiology.

Methods

Study population

The prospective KACLiF study is a Korean, multicentre, prospective, observational study performed in 23 medical centres. Each hospital had a liver unit, specific ward(s) for liver patients and intensive care units, and all of them had access to an LT program. Patients were screened and enrolled from July 2015 to August 2018. A total of 1,773 patients who were admitted for the treatment of AD, of whom 272 cases were excluded because these had been cases of recurrent hospitalization during the follow-up period after first enrolment and 1,501 patients who were included at the first hospitalization during the study period, were analysed. AD

was defined as overt ascites, overt hepatic encephalopathy, GI bleeding, any kind of bacterial infection and the deterioration of liver dysfunction, defined as a serum bilirubin level ≥3 mg/dL. All instances of overlapping AD events were included and duly recorded.LC was defined as (1) a cirrhotic configuration of the liver and/or splenomegaly in radiologic findings, (2) varices (abnormally enlarged veins, detected by upper endoscopy or cross-sectional images), (3) biochemical parameters such as platelet, albumin, bilirubin and prothrombin time and (4) historical confirmation such as diffuse nodulation of liver and fibrous bands [10]. Patients who met any of the following criteria were excluded: (1) age <18 years, (2) the absence of any chronic liver disease, (3) the presence of non-hepatic malignancy, (4) admission due to chronic illness unrelated with CLD, (5) human immunodeficiency virus infection, (6) chronic decompensation of end-stage liver disease, (7) less than 28 days of follow-up and (8) incomplete data. This study protocol was approved by the Institutional Review Boards of all 23 participating academic centres. Written informed consent was obtained from patients or their legal surrogates if we could not obtain consent from patients before enrolment in this study.

Data collection and definition of clinical parameters

Data on patient demographics, the aetiology of liver disease, clinical and laboratory variables, types of AD and the development of ACLF were collected. The viral hepatitis-related CLD and autoimmune-related CLD were defined as the definitive viral serology and biochemical parameters and/or liver pathology as diagnostic criteria [11–13]. And the aetiology for alcohol related CLD was defined in patients who had taken more than moderate drinking of alcohol (14 units/week for men and 7 units/week for women) with alcohol use disorder at the time of the diagnose for the CLD [14, 15].

Precipitating events included any kind of bacterial infection, GI bleeding, active alcoholism, reactivation of viral hepatitis, toxic liver injury and others. Active alcoholism was defined as more than 14 units/week for men and more than 7 units/week for women within 3 months prior to admission. Systemic inflammatory response syndrome (SIRS) was defined according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine [16]. The Child-Turcotte-Pugh (CTP) score (serum bilirubin, albumin, prothrombin time, grade of ascite and hepatic encephalopathy), Model for End-Stage Liver Disease (MELD) score (serum bilirubin, creatinine and prothrombin time) and Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score (serum bilirubin, prothrombin time, creatinine, Pa02/FiO2, mean arterial pressure and grade of hepatic encephalopathy) were calculated based on the clinical variables within 24 h of admission. The patients who developed AD and organ failure were classified as having ACLF according to the CLIF-C definition [17].

Primary outcomes and follow-up

The primary endpoints of this study were 28-day and overall adverse outcomes during the follow-up period. Adverse outcomes were defined as death or LT. Person-years were censored on the date of death, LT or the last date of follow-up, whichever came first. In order to both the mortality and the occurrence of LT in patients, the patient's medical records were utilized in conjunction with national mortality data. The subgroup analysis was performed to investigate the prognostic difference on the presence of cirrhosis and ACLF.

Statistical analyses

Continuous variables were summarized as the means ± standard deviations or medians and ranges and compared using Student's *t* test or the Mann–Whitney *U* test. Discrete variables were summarized as the number of events for each category and percentages and compared using the $\chi 2$ test or Fisher's exact test, as appropriate. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox regression analysis was conducted for factors associated with survival. Multiple Cox regression analysis was carried out using variables that showed an association in univariate analysis with a p value < 0.1 and performed using a forward conditional stepwise procedure to avoid multicollinearity. Statistical analyses were performed using SPSS for Windows, version 27.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics according to aetiology of chronic liver disease

The baseline characteristics according to aetiology of 1,501 patients with AD of CLD are shown in Table 1. There was a median follow-up of 8.0 months (1.0–16.0 months), the mean age was 54.7 years, and males accounted for 74.5%. LC was confirmed in 93.2% of patients. The median CPS and MELD scores were 9.0 (7.0–11.0) and 17.0 (12.9–22.3), respectively. The common AD events were GI bleeding

(35.3%) and jaundice (35.0%). Overall adverse outcomes (death or LT) during the follow-up period occurred in 339 patients (22.6%). The most common aetiology was alcohol-related CLD (68.0%), followed by viral hepatitis CLD (13.7%), viral hepatitis with alcohol-related CLD (8.6%), cryptogenic CLD (7.2%) and autoimmune-related CLD (AIH or PBC) (2.5%).

Patients with alcoholic CLD were predominantly male, had a high rate of active alcoholism and consumed larger amounts of alcohol than patients with other aetiologies ($p < 0.05$). And the history of previous AD was higher per cent in alcoholic-related CLD and cryptogenic CLD than viral hepatitis with alcohol-related CLD ($p < 0.05$).

Patients with viral hepatitis with alcohol-related CLD showed the worst liver function profiles in CPS and MELD scores with poor prognosis at 28 days and overall adverse outcomes (12.4% and 31.0%, $p < 0.05$, respectively) compared with others. LT was performed most often among patients with viral hepatitis with alcohol-related CLD in the 28-day period, but there was no difference in the LT rate between patients with

Table 1. Baseline characteristics according to the aetiology of AD of chronic liver disease.

	Overall (*N* = 1501)	Virus (HBV+HCV) (*N* = 206)	Alcohol (*N* = 1021)	Virus + alcohol (*N* = 129)	AIH/PBC (*N* = 37)	Cryptogenic (*N* = 108)	*p* value
Age (years)	54.7 ± 11.5	56.3 ± 12.7*	53.4 ± 10.4	52.0 ± 9.9	61.7 ± 13.3*	65.5 ± 12.2*	<0.001
Male (*n*, %)	1118 (74.5)	121(58.7)*	828(81.1)	115(89.1)	8(21.6)*	46(42.6)*	<0.001
AD (*n*, %)[+]							
Ascites	431 (29.1)	39 (18.9)*	314 (30.8)	41 (31.8)	12 (32.4)	31 (28.7)	0.015
Bacterial infection	132 (8.8)	17 (8.3)	91 (8.9)	13 (10.1)	4 (10.8)	7 (6.5)	0.867
Varix bleeding	429 (28.6)	56 (27.2)	302 (29.6)	36 (27.9)	7 (18.9)	28 (25.9)	0.594
Non-varix bleeding	100 (6.7)	8 (3.9)	76 (7.4)	8 (6.2)	1 (2.7)	7 (6.5)	
HE	222 (14.8)	22 (10.7)	155 (15.2)	16 (12.4)	4 (10.8)	25 (23.1)*	0.042
Jaundice	525 (35.0)	88 (42.7)	359 (35.2)	44 (34.1)	16 (43.2)	18 (16.7)*	<0.001
Cirrhosis (*n*, %)	1399 (93.2)	160 (77.7)*	981 (96.1)	122 (94.6)	36 (97.3)	100 (92.6)	<0.001
Previous AD[^] (*n*, %)	448 (29.8)	39 (18.9)	334 (32.7)*	30 (23.3)	6 (16.2)	39 (36.1)*	<0.001
CVD (*n*, %)	67 (4.5)	5 (2.4)	47 (4.6)	3 (2.3)	4 (10.8)	8 (7.4)	1.00
DM (*n*, %)	382 (25.4)	54 (26.2)	241 (23.6)	26 (20.2)	11 (29.7)	50 (46.3)	1.00
HTN (*n*, %)	319 (21.3)	38 (18.4)	193 (18.9)	27 (20.9)	11 (29.7)	50 (46.3)	1.00
PE (*n*, %)							
Alcoholism	738 (49.2)	6 (2.9)*	660 (64.6)*	70 (54.3)	1 (2.7)*	1 (0.9)*	<0.001
Bacterial infection	101 (6.7)	23 (11.2)	61 (6.0)	7 (5.4)	3 (8.1)	7 (6.5)	0.097
GI bleeding	355 (23.6)	54 (26.2)	241 (23.6)	29 (22.5)	6 (16.2)	25 (23.1)	0.276
Viral activation[$]	66 (4.4)	55 (26.7)*	1 (0.1)*	6 (4.7)	0	4 (3.7)	<0.001
Toxic	21 (1.4)	7 (3.4)	9 (0.9)	2 (1.6)	1 (2.7)	2 (1.9)	0.072
Others	64 (4.3)	8 (3.9)	26 (2.5)	4 (3.1)	10 (27.0)*	16 (14.8)*	<0.001
Alcohol intake[#] (*n*, %)	967 (64.4)	29 (14.1)*	827 (81.0)	98 (76.0)	5 (13.5)*	8 (7.4)*	<0.001
Alcohol amount (g/day)	63.2 ± 81.5	10.1 ± 57.6)*	80.7 ± 79.4	75.7 ± 104.3	10.0 ± 29.0)*	4.6 ± 20.3)*	<0.001
SIRS (*n*, %)	356 (23.7)	33 (16.0)*	27 (26.4)	34 (26.4)	3 (8.1)*	16 (14.8)*	<0.001
HCC (*n*, %)	63 (4.2)	11 (5.3)	36 (3.5)	7 (5.4)	0 (0)	9 (8.3)	0.070
Laboratory data							
WBCx10^3/L	8.19 (4.80–9.94)	6.13 (4.28–8.88)	7.25 (5.02–10.62)	6.72 (4.83–9.47)	5.58* (4.26–7.99)	5.54 (4.18–7.73)*	<0.001
Haemoglobin, g/dL	10.7 (8.6–12.4)	11.6 (9.6–13.3)	10.5 (8.4–12.2)*	11.1 (8.7–13.1)	11.1 (9.4–12.3)	10.4 (8.7–11.7)	<0.001
Platelet, mg/L	96 (65–143)	104 (63–154)*	95 (65–143)*	82 (58–126)	116 (91–166)*	99 (69–150)*	0.018
Bilirubin, mg/dL	3.6 (1.6–8.2)	3.0 (1.3–8.4)*	3.9 (1.8–8.4)	4.5 (1.7–10.8)	2.7 (0.7–6.2)*	1.6 (0.8–3.7)*	<0.001
Albumin, g/dL	2.9 (2.5–3.3)	3.2 (2.7–3.6)*	2.8 (2.5–3.3)	2.8 (2.4–3.3)	3.0 (2.5–3.7)	2.9 (2.6–3.2)	<0.001
INR	1.5 (1.3–1.8)	1.4 (1.3–1.7)*	1.5 (1.3–1.8)	1.5 (1.3–2.1)	1.3 (1.1–1.5)*	1.4 (1.2–1.6)*	<0.001
Creatinine, mg/dL	0.9 (0.7–1.2)	0.8 (0.7–1.0)*	0.9 (0.7–1.3)	0.9 (0.7–1.1)	0.7 (0.6–1.0)*	1.0 (0.7–1.3)	<0.001
Sodium, mEq/L	136 (132–139)	137 (134–140)	135 (131–139)	135 (132–139)	137 (132–140)	137 (133–140)	<0.001
Child-Pugh score	9.0 (7.0–11.0)	8.0 (7.0–10.0)*	9.0 (8.0–11.0)	9.0 (8.0–11.0)	7.0 (7.0–9.0)*	8.0 (7.0–9.0)*	<0.001
MELD score	17.0 (12.9–22.3)	15.7 (11.6–20.3)*	17.4 (13.7–22.7)	18.1 (12.6–25.2)	13.5 (9.7–17.2)*	13.7 (10.9–18.7)*	<0.001
MELD-Na score	19.8 (14.8–25.7)	17.8 (14.0–23.6)*	20.7 (15.6–26.4)	20.9 (14.8–27.6)	15.8 (11.6–20.3)*	17.0 (12.2–22.1)*	<0.001
Adverse outcome (*n*, %)							
28 days	81 (5.4)	12 (5.8)*	49 (4.8)*	16 (12.4)	1 (2.7)	3 (2.8)*	0.004
LT	14 (0.9)	4 (1.9)	4 (0.3)	5 (3.9)	0	1 (0.9)	
90 days	166 (11.1)	27 (13.1)*	103 (10.1)*	26 (20.2)	3 (8.1)*	7 (6.5)*	0.004
LT	30 (2.0)	10 (4.9)	12 (1.2)	7 (5.4)	0	1 (0.9)	
Overall	339 (22.6)	37 (18.0)*	234 (22.9)*	40 (31)	5 (13.5)	23 (21.3)*	0.047
LT	43 (2.9)	11 (5.3)	22 (2.2)	7 (5.4)	1 (2.7)	2 (1.8)	

*It is indicated a significant difference compared to viral hepatitis with alcohol related CLD ($p<0.05$).
[+]all duplicate events that occurred were included.
[^]The history of acute decompensation occurred within 1 year.
[&]It is included viral activation of hepatitis virus B, hepatitis virus C and hepatitis virus A.
[#]Current alcohol intake within 3 months.
AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; AD, acute decompensation; GI, gastrointestinal; HE, hepatic encephalopathy; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; PE, precipitating event; HCC, hepatocellular carcinoma; SIRS, systemic inflammatory response syndrome; WBC, white blood cell; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease.

viral hepatitis with alcohol-related CLD and those with viral hepatitis CLD in the overall period (5.4% vs. 5.3%).

28-day adverse outcomes and associated factors of AD of chronic liver disease

Overall, 28-day adverse outcomes occurred in 81 patients (5.4%). The associated factors for 28-day adverse outcomes among all patients are shown in Table 2. In univariate analysis, the aetiology of CLD, SIRS and MELD score was significant factors for 28-day adverse outcomes. In multivariable analysis, the aetiology of CLD was a significant factor for 28-day adverse outcomes ($p = 0.012$) stratified by the presence of SIRS, serum albumin and MELD score. The low albumin level, the presence of SIRS and a high MELD score were also significant risk factors for 28-day adverse outcomes. The aetiologies of CLD stratified by 28-day adverse outcomes were in order as follows: viral hepatitis with alcohol-related CLD (12.4%), viral hepatitis CLD (5.8%), alcohol-related CLD (4.8%), cryptogenic CLD (2.8%) and autoimmune-related CLD (2.7%) ($p = 0.003$) (Figure 1).

Subgroup analysis according to liver function and LC status: the effect of aetiology of CLD on 28-day adverse outcomes

In the group with LC ($n = 1,399$), viral hepatitis with alcohol-related CLD showed increased adverse outcomes, followed by viral hepatitis CLD, alcohol-related CLD and cryptogenic or autoimmune-related CLD ($p = 0.009$) (Table 3). In the MELD score ≥15 group ($n = 938$), the number of adverse outcomes was also increased among patients with viral hepatitis with alcohol-related CLD, followed by those with viral CLD, alcohol-related CLD and cryogenic or autoimmune-related CLD ($p = 0.001$).

Overall adverse outcomes and associated factors of AD of chronic liver disease

Overall adverse outcomes occurred in 339 patients (22.6%). The significant CLD aetiologies stratified by overall adverse outcomes were in order as follows: viral hepatitis with alcohol-related CLD (31.0%), alcohol-related CLD (22.9%), cryptogenic CLD (21.3%), viral hepatitis CLD (18.0%) and autoimmune-related CLD (13.5%) ($p = 0.010$) (Figure 2).

The associated factors for overall adverse outcomes are shown in Supplementary table 1. In multivariable analysis, serum albumin, history of AD, cirrhosis and MELD score were significant factors for overall adverse outcomes stratified by serum albumin, aetiology of CLD, history of AD, cirrhosis, SIRS and MELD score.

Subgroup analysis according to AD of liver cirrhosis and ACLF

We analysed patients with ACLF or organ failure according to the CLIF-C definition. Among 1,399 patients with LC, 250 (17.9%) patients showed ACLF at admission (Table 4). Viral hepatitis with alcohol-related CLD showed a high frequency and severity of ACLF and organ failure compared with other aetiologies. In the absence of ACLF group ($n = 1,149$), the aetiology of CLD was stratified by 28-day adverse outcomes in the following order: viral hepatitis with alcohol-related CLD, viral hepatitis CLD, cryptogenic CLD, alcohol-related

Table 2. Associated factors for 28-day adverse outcomes.

	Univariate HR (95% CI)	*p* value	Multivariate HR (95% CI)	*p* value
Age	1.000 (0.981–1.019)	0.972		
Sex	1.074 (0.659–1.753)	0.774		
Aetiology		0.003		0.012
Cryptogenic	Ref.		Ref.	
AIH/PBC	0.929 (0.097–8.931)		1.366 (0.141–13.185)	
Virus	2.075 (0.904–4.765)		1.806 (0.507–6.430)	
Alcohol	1.640 (0.763–3.527)		0.865 (0.266–2.812)	
Virus + alcohol	3.554 (1.543–8.189)		2.193 (0.632–7.613)	
Alcohol use	1.427 (0.880–2.313)	0.149		
Alcohol amount	1.484 (0.945–2.330)	0.086		
Total bilirubin	1.083 (1.064–1.101)	<0.001		
Albumin	0.285 (0.191–0.425)	<0.001	0.498 (0.329–0.753)	0.001
INR	1.330 (1.251–1.414)	<0.001		
Na	0.937 (0.912–0.964)	<0001		
Previous AD	0.800 (0.487–1.315)	0.379		
SIRS	2.648 (1.708–4.104)	<0.001	1.800 (1.148–2.823)	0.010
HCC	0.275 (0.038–1.978	0.200		
Cirrhosis	1.844 (0.582–5.842)	0.298		
MELD	1.148 (1.124–1.172)	<0.001	1.133 (1.108–1.159)	<0.001

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; AD, acute decompensation; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; SIRS, systemic inflammatory response syndrome.

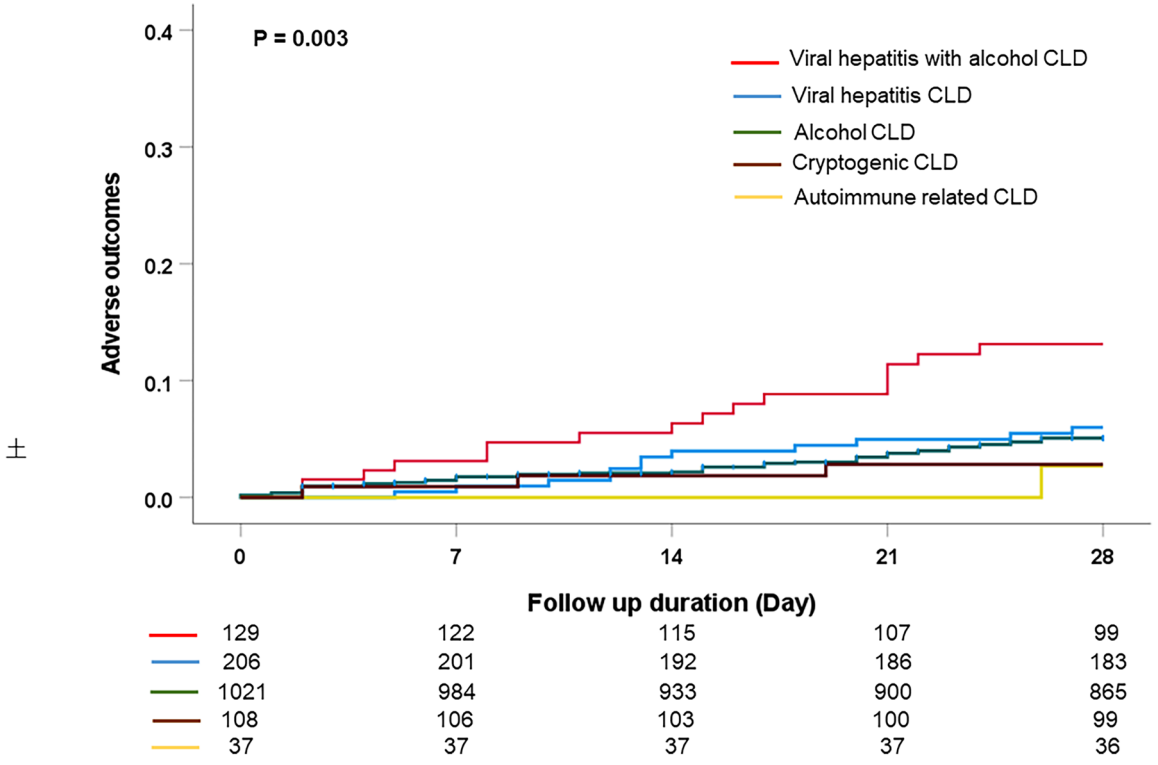

Figure 1. The 28-day adverse outcomes according to aetiology of chronic liver disease.

Table 3. Subgroup analysis according to liver function status.

	Virus	Alcohol	Virus + alcohol	AIH/PBC	Cryptogenic	
	28-day adverse outcome (%)	28-day adverse outcome (%)	28-day adverse outcome (%)	28-day adverse outcome (%)	28-day adverse outcome (%)	*p*
LC						
No (*n* = 102)	2/46 (4.3)	0/40 (0)	1/7 (14.3)	0/1 (0)	0/8 (0)	0.168
Yes (*n* = 1,399)	10/160 (6.2)	49/981 (5.0)	15/122 (12.3)	1/36 (2.8)	3/100 (3.0)	0.009
MELD						
<15 (*n* = 561)	0/92 (0)	5/335 (1.5)	0/46 (0)	0/23 (0)	0/65 (0)	0.474
≥15 (*n* = 938)	12/112 (10.7)	44/686 (6.4)	16/83 (19.3)	1/14 (7.1)	3/43 (7.0)	0.001

LC, liver cirrhosis; MELD, Model for End-Stage Liver Disease.

CLD and autoimmune-related CLD ($p = 0.006$). However, the aetiology of CLD was not stratified by adverse outcomes in the presence of ACLF group ($p = 0.473$). LT was performed most often among patients with viral hepatitis with alcohol-related CLD in the 28-day period, but there was no difference in the LT rate between patients with viral hepatitis with alcohol-related CLD and those with viral hepatitis CLD in the overall period (4.9% vs. 4.4%).

The comparison and subgroup analysis of patients with viral, alcohol or both aetiologies in LC

We compared the alcohol-related CLD, viral hepatitis CLD and viral hepatitis with alcohol-related CLD to clarify the effect of aetiologies for prognosis in patients with LC.

When comparing the three groups, the clinical characteristics of patients with viral hepatitis with alcohol-related CLD exhibited greater similarity to those with alcohol related CLD than to those with viral hepatitis CLD in terms of age, gender, the events of AD and liver function status (CPS, MELD) (Table 1). Furthermore, the incidence of ACLF also demonstrated an increased among patients with alcohol-related CLD and those with viral hepatitis with alcohol-related CLD in comparison with patients with viral hepatitis-related CLD ($p < 0.05$) (Table 4). In subgroup analysis according MELD score ≥15, 28-day adverse outcomes increased in following order: alcohol-related CLD (6.7%), viral hepatitis CLD (12.5%) and viral hepatitis with alcohol-related CLD (19.0%) (alcohol-related CLD vs. viral hepatitis with alcohol-related CLD, $p = 0.001$, viral hepatitis CDL vs. viral hepatitis with alcohol-related CLD, $p = 0.07$) (Figure 3).

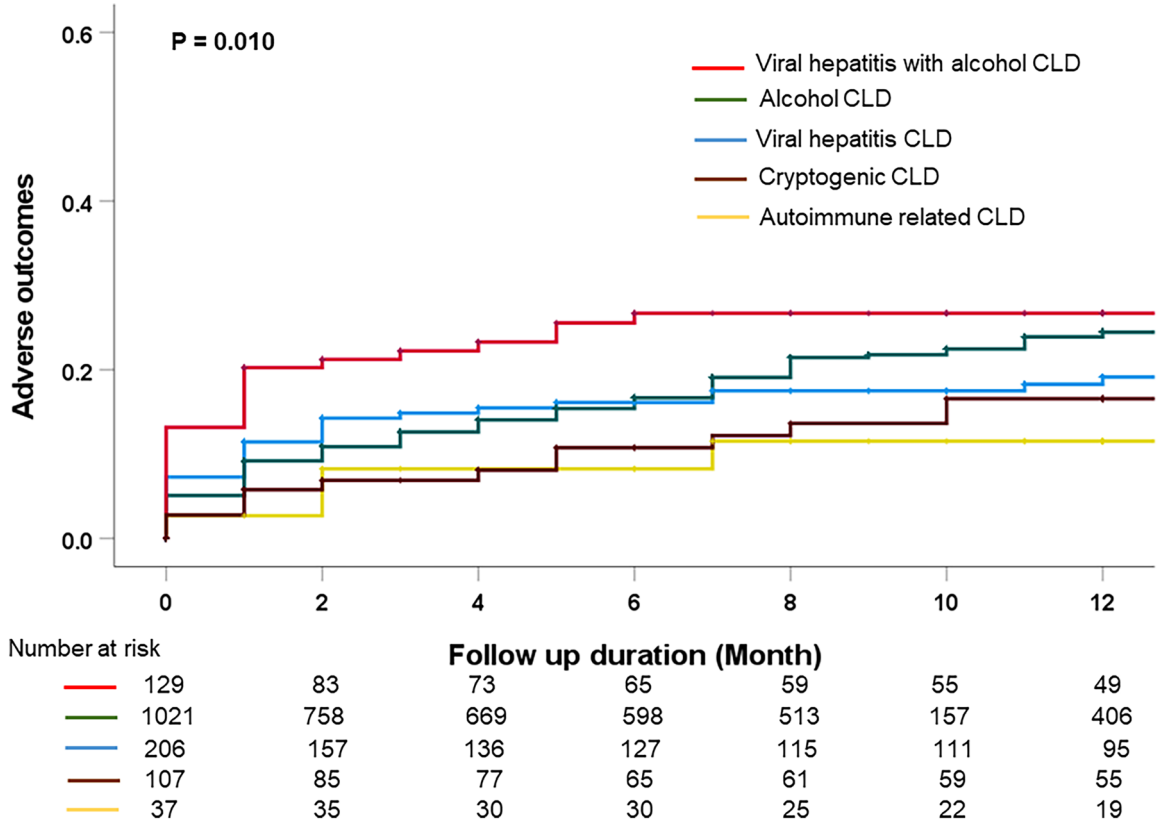

Figure 2. The overall adverse outcomes according to aetiology of chronic liver disease.

Table 4. Subgroup analysis according to AD on liver cirrhosis and ACLF.

	Overall (*N* = 1399)	Virus (HBV+HCV) (*N* = 160)	Alcohol (*N* = 981)	Virus + alcohol (*N* = 122)	AIH/PBC (*N* = 36)	Cryptogenic (*N* = 100)	*p* value
Age	55.1 ± 11.3	57.6 ± 11.8*	53.6 ± 10.4*	52.2 ± 9.9	61.9 ± 13.3*	67.0 ± 10.8	<0.001
Sex	1049 (75.0)	95 (59.4)*	798 (81.3)	109 (89.3)	7 (19.4)*	40 (40.0)*	<0.001
ACLF, *n* (%)	250 (17.9)	13 (8.1)*	192 (19.6)	27 (22.1)	2 (5.6)*	16 (16.0)	0.001
Gr 1	127 (9.1)	7 (4.4)	93 (9.5)	12 (9.8)	2 (5.6)	13 (13.0)	0.001
Gr 2	80 (5.7)	4 (2.5)	65 (6.6)	9 (7.4)	0 (0)	2 (2.0)	
Gr 3	43 (3.1)	2 (1.3)	34 (3.5)	6 (4.9)	0 (0)	1 (1.0)	
Child-Pugh score	9.0 (7.0–11.0)	8.0* (7.0–10.0)	9.0 (8.0–11.0)	9.0 (8.0–11.0)	7.0* (7.0–9.0)	8.0* (7.0–9.0)	<0.001
MELD score	16.8 (12.7–22.3)	15.0 (11.0–2.03)*	17.4 (13.6–22.7)	18.1 (12.7–25.3)	13.2 (9.6–17.2)*	13.6 (10.8–18.0)*	<0.001
MELD-Na score	19.8 (14.7–25.8)	17.3* (12.5–23.6)	20.5 (15.5–26.4)	21.1 (14.8–28.0)	15.3 (11.5–20.2)*	16.4 (12.0–21.9)*	<0.001
CLIF-C OF score	7.0 (6.0–8.0)	7.0 (6.0–8.0)*	7.0 (6.0–8.0)	7.0 (6.0–8.3)	6.0 (6.0–7.0)*	6.5 (6.0–7.0)*	<0.001
Liver, *n* (%)	212 (15.2)	22 (13.8)	160 (16.3)	26 (21.3)	2 (5.6)	2 (2.0)	<0.001
Kidney, *n* (%)	135 (9.6)	8 (5.0)	104 (10.6)	11 (9.0)	1 (2.8)	11 (11.0)	0.126
Brain, *n* (%)	113 (8.1)	5 (3.1)	90 (9.2)	8 (6.6)	0 (0)	10 (10.0)	0.028
Circulation, *n* (%)	60 (4.3)	3 (1.9)	51 (5.2)	3 (2.5)	0 (0)	3 (3.0)	0.123
Respiratory, *n* (%)	21 (1.5)	0	18 (1.8)	2 (1.6)	0 (0)	1 (1.0)	0.418
Coagulation, *n* (%)	112 (8.0)	8 (5.0)	75 (7.6)	24 (19.7)	(2.8)	4 (4.0)	<0.001
Adverse outcome, *n* (%)							
28-day mortality	78 (5.6)	10 (6.3)	49 (5.0)*	15 (12.3)	1 (2.8)	3 (3.0)*	0.011
LT	12 (0.9)	3 (1.9)	4 (0.4)	4 (3.3)	0	1 (1.0)	
90-day mortality	159 (11.4)	22 (13.8)	102 (10.4)*	25 (20.5)	9 (8.3)	7 (7.0)*	0.007
LT	25 (1.8)	6 (3.8)	12 (1.2)	6 (4.9)	1 (2.8)	0	
Overall mortality	332 (23.7)	32 (20.0)*	233 (23.8)*	39 (32.0)	5 (13.9)*	23 (23.0)	0.030
LT	38 (2.7)	7 (4.4)	22 (2.2)	6 (4.9)	1 (2.8)	2 (2.0)	

*It is indicated a significant difference compared to viral hepatitis with alcohol-related CLD ($p<0.05$).
ACLF, acute-on-chronic liver failure; MELD, CLIF-C, Chronic Liver Failure-C; LT, liver transplantation.

Discussion

Acute decompensation (AD), especially accompanied by dysfunction of other organs, is a common cause of adverse outcomes (death or LT) in CLD. In this study, the clinical characteristics by CLD aetiology were summarized among prospectively enrolled CLD patients with AD, and the effect of CLD aetiology on short-term and long-term adverse outcomes was confirmed among these patients. The baseline characteristics

were different according to the five different aetiologies of CLD: viral hepatitis, alcohol-related CLD, viral hepatitis with alcohol-related CLD, autoimmune-related CLD and cryptogenic CLD. The difference in the aetiology of CLD stratified by adverse outcomes was statistically significant. Notably, patients with viral hepatitis with alcohol-related CLD showed poorer liver function profiles and increased 28-day/overall adverse outcomes than patients with other aetiologies.

HBV and HCV are known leading causes of CLD and the development of HCC. Currently, the vast majority of HCV-infected patients treated with direct-acting antivirals reach a sustained virological response rate, and HBV-infected patients treated with nucleoside/nucleotide agents achieve at least viral suppression within almost 1 year [11, 12]. However, alcohol-related liver disease still causes increasing morbidity and mortality of CLD [5]. The process of alcohol-related liver damage is complex and multifactorial. In particular, the interaction of viral hepatitis and alcohol-related liver damage is not fully understood, but alcohol affects the major histocompatibility complex (MHC-I and MHC-II), which acts in antigen presentation and has direct and indirect negative effects on viral replication [18]. Additionally, alcohol increases both oxidative stress and cytotoxicity and weaknesses the immune response to hepatitis virus [18]. The negative synergistic effect of alcohol and viral hepatitis on patients leads to a poor prognosis, accelerating the progression of liver damage in addition to the toxicity of alcohol itself. In a previous study, the AD of alcoholic LC and alcoholic hepatitis showed the highest mortality with active alcoholic patients in several weeks [19, 20]. In addition, the AD of alcohol-related liver disease often shows SIRS even in the absence of an infection. SIRS with or without infection is a major determinant of multiorgan failure and mortality in alcoholic hepatitis [21]. Patients with alcohol-related CLD showed a higher proportion of SIRS (26.4%) than patients with other aetiologies in this prospective cohort. SIRS is also an important factor for 28-day adverse outcomes along with age, aetiology and MELD score. Furthermore, in this study, the clinical characteristics of viral hepatitis with alcohol-related CLD were similar to alcohol related CLD, but in cirrhotic patients with high MELD, viral hepatitis with alcohol-related CLD demonstrated a poorer prognosis compared to viral hepatitis CLD or alcohol-related CLD. This clinical observation underscores a negative synergistic effect of viral infection and alcohol. Previous studies have shown good long-term prognosis in patients with alcohol abstinence in alcoholic cirrhosis/alcoholic hepatitis, although the duration of abstinence is controversial [22–24]. Our findings suggested that the occurrence of alcohol-induced CLD combined with viral hepatitis itself has a poor long-term prognosis for AD compared to other aetiology, regardless of subsequent alcohol abstinence. In light of this, individuals diagnosed with viral hepatitis should refrain from consuming moderate amounts of alcohol as early as possible, as it has the potential to induce chronic liver injury.

The differences in short-term adverse outcomes according to aetiology occur also depending on whether the cause of AD and CLD is treated. In viral hepatitis CLD, viral activation accounts for only 26.7% of precipitating factors for AD in this study. AD in chronic hepatitis B patients who initiated antiviral therapy for viral remission required several months to achieve remission [11], as alcohol use is a factor that cannot be easily corrected in the occurrence of AD and viral activation poses a challenge in terms of rapid control, unlike gastrointestinal bleeding or infection, both of which can be promptly managed within a short timeframe. For this reason, viral hepatitis can be considered to have increased 28-day adverse outcomes with alcohol-related CLD in this study. However, overall

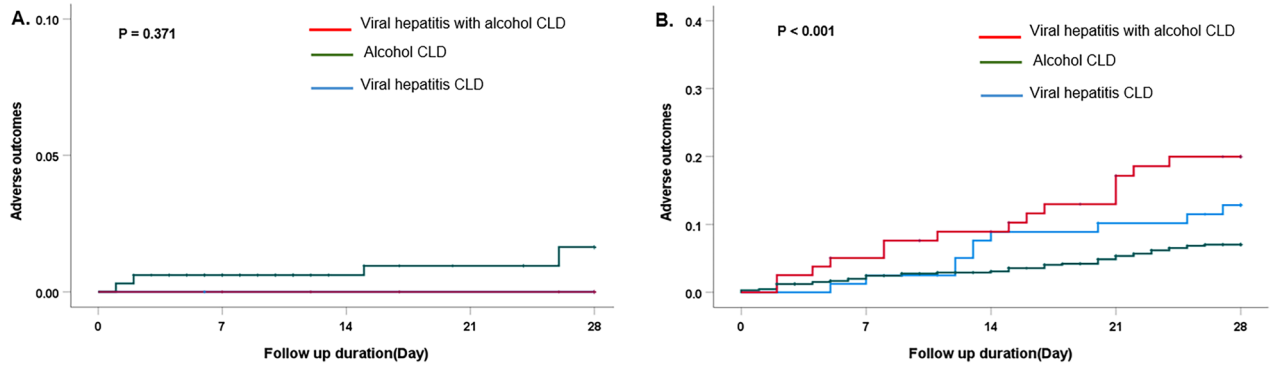

Figure 3. **A**) The 28-day adverse outcomes according to aetiology of cirrhotic patients with MELD < 15 and B) the 28-day adverse outcomes according to aetiology of cirrhotic patients with MELD ≥15.

adverse outcomes were more increased in alcohol-related CLD and cryptogenic CLD (mostly NAFLD) than in viral hepatitis and autoimmune CLD. Overall adverse outcomes were only affected by older age, liver function status and the frequency of AD in multivariate analysis.

In this study, the MELD score was the highest among patients with viral hepatitis with alcohol-related CLD. Patients with viral hepatitis with alcohol-related CLD had a high proportion of LT (3.9%) compared with patients with other aetiologies in the 28-day follow-up period. However, during the overall period, these patients showed the worst adverse outcomes, but the proportion of LT (5.4%) was similar to that of viral hepatitis patients (5.3%). These results were comparable even in the subgroup for cirrhosis. The MELD score was introduced for the prioritization of LT candidates in 2002 [25]. During this period, MELD scores predicted 90-day mortality from various liver diseases, and the allocation algorithm followed by MELD score was shown to reduce waiting list mortality and improve patient survival [26–28]. However, the prognostic capacity of MELD score for predicting 90-day mortality has somewhat diminished in the contemporary era. Godfrey et al. analysed 120,393 patients listed for LT in the United Network for Organ Sharing (UNOS) system from 2002 to 2016 [29]. The incidence of patients with HCV-related liver disease on the waiting list decreased, but the incidence of alcoholic liver disease and nonalcoholic fatty liver disease increased from 2002 to 2016. Moreover, the MELD score incorrectly predicts mortality in about 15–20% of patients because the score does not include major cirrhotic complication that induced poor prognosis [27]. Other scoring system, the CLIF Consortium Acute Decompensation score (CLIF-C ADs) developed by European prospective cohort for cirrhotic patients composed with age, creatinine, white blood cell count and INR is more accurate than MELD score in predicting prognosis in AD of cirrhotic patients [17]. For these reasons, there is a pressing need to reevaluate the criteria used in allocating LT, particularly MELD score. This reassessment should take into account the shifting prevalence rates, therapeutic advancements impacting disease prognosis and severity across different aetiologies, with special attention to patients with AD.

Among the 1,399 cirrhotic patients with AD of CLD, 250 (17.9%) had ACLF at admission. The proportion of ACLF according to aetiology was higher in viral hepatitis with alcohol-related CLD (22.1%), alcohol-related CLD (19.6%) and cryptogenic CLD (16.0%) than in viral hepatitis (8.1%) or autoimmune-related CLD (5.6%). The mechanism of ACLF in alcohol liver disease that induces multiorgan failure and high mortality is explained by elevated systemic inflammation and circulating cytokine and innate/adaptive immune cell dysfunction [20]. The differences in the pattern of ACLF between alcohol-related liver disease and cryptogenic CLD were the type of organ failure and grade of ACLF. Alcohol-related liver disease was dominant in liver failure and showed more severe ACLF grade than cryptogenic CLD in this study. Non-alcoholic steatohepatitis (NASH) was the most common aetiology of cryptogenic LC [30]. Compared to patients with other aetiologies, despite the relatively high ACLF proportion of cryptogenic LC, the 28-day adverse outcomes were lower than those among patients with other aetiologies. This finding could be explained by the higher burden of comorbidities among NASH patients, which itself was a protective factor for short-term mortality and showed a lower ACLF grade than other aetiologies [30].

Our data have some limitations. The overall median duration of this study was relatively short, at 8 months. Therefore, we lacked data comparing a greater number of 1-year adverse outcomes between patients with different aetiologies. Nonetheless, this duration was deemed sufficient for meaningful observation of differences in short-term adverse outcomes according to aetiology among patients with AD of CLD. The patient with AD of CLD in alcohol-related liver disease did not undergo liver biopsy. Consequently, we were unable to distinguish whether some cases of alcohol-induced acute-on-chronic liver failure (ACLF) represented a severe form of alcoholic liver disease or were merely a clinical progression of severe alcoholic hepatitis, which constitutes a catastrophic progression of alcoholic liver disease associated with high mortality [31]. Finally, we analysed the significance of aetiology in predicting the prognosis of AD of CLD. This cohort was composed of Asian individuals. To validate the significance of aetiology, further prospective comparative studies involving participants from diverse racial backgrounds and continental cohorts may be warranted. However, the major strength of this study lies the large number of patients with complete data in prospective study settings. This is the first prospective study to compare the adverse outcomes of the AD of CLD according to the various aetiologies. Specifically, we were able to elucidate a fragment of knowledge gleaned from previous studies, namely, the poor prognosis of alcohol use in viral liver disease, by directly comparing adverse outcomes between viral hepatitis with alcohol-related CLD and alcohol/viral-related CLD.

In conclusion, viral hepatitis with alcohol-related CLD showed the worst adverse outcomes compared with other aetiologies, such as viral hepatitis, alcohol-related CLD, cryptogenic CLD and autoimmune-related CLD, in AD of liver disease even among individuals presenting with high MELD scores. Patients diagnosed with viral hepatitis should refrain from alcohol consumption to prevent the development of alcohol-related liver disease, as it significantly worsens overall adverse outcomes in cases of AD.

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Authors contributions

J.H.K. and S.E.K. conceptualized the study and contributed to writing of the original draft; J.H.K and D.J.K. contributed to writing, review and editing; K.J.H., H.Y.K., D.S.S., E.L.Y. and T.H.K. contributed to data curation; J.W.P., H.-S.K. and K.T.S. contributed to funding acquisition; S.W.N., Y.-K.J., S.-H.K., S.-W.J., S.-G.K., J.-J.Y., G.J.C., D.H.S., H.Y.K, W.J.J. and I.H.K. contributed to resources; H.-J.Y., J.-H.K., J.Y.J., S.-W.L., J.-Y.J., Y.S.S., K.M.Y., H.A.L., J.I.S., J.-H.K., H.B.C., J.-H.S., J.Y.K., J.Y.C., Y.J.K., J.M.Y., J.G.P., W.K. and H.J.C. carried out investigation; K.J.H. and B.S.K. contributed to formal analysis; J.-M.Y., W.K. and D.J.K. supervised the study; J.Y.J., J.-J.Y., B.S.K. and W.J.K. contributed to methodology.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Hallym University Medical Center (2015-I071,date of approval: 4.Aug.2015).

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The ability to share access with others if certain requirements is met.

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