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Original Article

Liver Failure versus Organ Failure in Acute-on-Chronic Liver Failure: Sequence and Consequence

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Background/Aims: Acute-on-chronic liver failure (ACLF) is characterized by the acute decompensation of the liver in patients with preexisting chronic liver disease or cirrhosis, often resulting in multiorgan failure and high short-term mortality. This study aimed to investigate the sequence of organ failures, particularly liver and renal failure, and their impact on the short-term survival in ACLF patients.

Methods: We analyzed data from 1,765 patients in a prospective Korean ACLF cohort, focusing on the timing of liver and renal failures. Overall survival (OS) was assessed using Kaplan-Meier survival analysis with the log-rank test, and multivariate analysis was performed using a Cox proportional hazards model.

Results: Patients with initial liver failure had significantly worse OS compared to those without liver failure (adjusted hazard ratio [aHR], 3.6; p=0.008), and those who developed liver failure during the disease course had an even poorer prognosis (aHR, 5.7; p=0.002). There was no significant difference in OS between patients without renal failure and those with initial renal failure (aHR, 0.8; p=0.508). However, renal failure that developed during hospitalization was associated with a worse prognosis (aHR, 1.9; p=0.056). Patients with initial renal failure had significantly better OS than those with initial liver failure (aHR, 2.4; p=0.040).

Conclusions: Organ failure developing during hospitalization is more detrimental than failure present at admission. ACLF with initial renal failure has a better prognosis than ACLF with initial liver failure. ACLF patients with initial renal failure have a 28-day survival rate exceeding 90% if renal failure is present initially; however, this rate significantly decreases if renal failure occurs during hospitalization. **(Gut Liver, 2026;20:837-847)**

Key Words: Acute-on-chronic liver failure; Renal failure; Organ failure

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by the acute decompensation of chronic liver disease or cirrhosis, and it is often accompanied by other organ failure. ACLF is similar to decompensated cirrhosis, which can result from various insults such as sepsis and active alcoholism in patients with underlying chronic liver

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disease or cirrhosis. However, ACLF differs in terms of its high short-term mortality rate, more closely resembling acute liver failure.[1]

Several different definitions of ACLF have been proposed by various academic societies. In 2009, the Asian Pacific Association for the Study of the Liver (APASL) provided the first consensus on ACLF, which was updated in 2019. They defined ACLF as an acute hepatic insult presenting with jaundice and coagulopathy and complicated by ascites or encephalopathy within 4 weeks.[2] In this definition, the target population includes patients with acute liver deterioration who have previously diagnosed or undiagnosed chronic liver disease, including cirrhosis; however, it excludes patients with prior decompensation of cirrhosis. By contrast, the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) consortium defines ACLF as an acute decompensation of cirrhosis in patients who meet prespecified criteria for organ failure according to the CLIF-Sequential Organ Failure Assessment (SOFA) scale.[3] The APASL and EASL-CLIF have different definitions of organ failure. The APASL defines liver failure as a total bilirubin concentration of ≥5 mg/dL and an international normalized ratio (INR) of ≥1.5, whereas the EASL-CLIF uses a cutoff value of 12 mg/dL for the total bilirubin concentration in liver failure and 2.5 for the INR in coagulation failure. For renal failure, the APASL employs the Acute Kidney Injury Network criteria or a threshold of 1.5 mg/dL for creatinine in the absence of baseline creatinine, while the EASL-CLIF uses a cutoff of 2.0 mg/dL.

The complex pathophysiology of ACLF, which involves systemic inflammation and immune dysregulation, contributes to the development of multiple organ failure, further complicating the clinical course and prognosis.[4] Previous studies have primarily focused on the presence and number of organ failures as well as their impact on clinical outcomes in patients with ACLF. Among the various organ failures that occur in ACLF, liver and renal failures are particularly significant because they are often the first to manifest and are associated with a poor prognosis.[5] However, the sequence in which these organ failures occur and their cumulative impact on the progression of ACLF are not well understood.

The aim of this study was to investigate the sequence of organ failures in patients with ACLF, specifically focusing on liver failure and renal failure, to determine their impact on the short-term prognosis. We also compared different cutoff values for organ failure in ACLF.

MATERIALS AND METHODS

1. Study population

This study included patients from the prospective Korea Acute-on-Chronic Liver Failure (pKACLiF) cohort. This cohort comprised patients with chronic liver disease who were hospitalized in 31 academic hospitals in Korea for treatment of acute deterioration of liver disease from October 2015 to May 2019. Acute deterioration of chronic liver disease was defined as the development of ascites, hepatic encephalopathy, gastrointestinal bleeding, or bacterial infection according to the EASL-CLIF consortium criteria.[3] The etiologies of underlying chronic liver disease included chronic hepatitis B, chronic hepatitis C, alcohol-associated liver disease, nonalcoholic fatty liver disease, and autoimmune liver disease. Cirrhosis was diagnosed either histologically or based on clinical findings such as radiological or laboratory results. Patients from the pKACLiF cohort who were diagnosed with ACLF either at the time of admission or by hospital day 7 were included in the study. The exclusion criteria were an age of <18 years, absence of cirrhosis, presence of radiologically confirmed hepatocellular carcinoma, hospitalization for extrahepatic disease, and human immunodeficiency virus infection. In total, 1,765 patients were screened, and 339 patients with ACLF were enrolled in the study (Supplementary Fig. 1).

This study was conducted with approval from the institutional review boards at each participating center (IRB approval number: 2015-06-010). Informed consent was obtained from all subjects, and for those incapable of providing consent, approval was secured from legally authorized representatives.

2. Data collection and definitions

We collected data on patient demographics, medical history, potential precipitating factors for hospitalization, laboratory measurements, and the development of organ failure. Clinical data within 24 hours of admission and 7 days (range, 5–9 days) after admission were collected.

Organ failures were categorized according to the EASL-CLIF consortium definition, based on the CLIF-SOFA score. Specifically, liver failure was defined as fulfillment of one or more of the following criteria: total bilirubin level of ≥12 mg/dL, INR of ≥2.5, or grade 3–4 hepatic encephalopathy. Renal failure was defined as a serum creatinine level of ≥2.0 mg/dL. Additionally, we employed a lower threshold for organ failure based on the APASL consensus, and in this study, we referred to organ failure defined by these criteria as liver dysfunction (total bilirubin ≥5 mg/dL, INR ≥1.5, or grade 1–2 hepatic encephalopathy) and renal dysfunction (serum creatinine ≥1.5 mg/dL).[2]

3. Statistical analysis

The primary outcome was 28-day survival. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as number (%). Categorical variables were analyzed using the chi-square test or Fisher exact test, and continuous variables were analyzed using the Student t-test. The 28-day survival rate was calculated using the Kaplan-Meier method, and survival differences were compared using the log-rank test. A Cox proportional hazards regression model was used to adjust for confounding factors influencing survival. Specifically, CLIF-SOFA score and age were adjusted to control for the impact of organ failure other than liver or renal failure on short-term prognosis. A p-value of <0.05 was considered statistically significant. Statistical tests were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline characteristics of the study population

Table 1 shows the baseline characteristics of the study population, which comprised 339 patients. The patients were stratified into four groups based on the ACLF grade: grade 0 (n=35), grade 1 (n=154), grade 2 (n=94), and grade 3 (n=56). Patients with grade 0 ACLF were initially admitted without ACLF but progressed to ACLF during hospitalization (between hospital days 5 and 9). The patients' mean age was 54.72 years, and most were male (75.81%). As the severity of ACLF increased, the blood pressure tended to decrease and the respiratory rate increased. The serum albumin level decreased with ACLF severity, while total bilirubin, alanine aminotransferase, and aspartate aminotransferase levels notably increased with higher ACLF grades. The prothrombin time–INR and creatinine level increased with ACLF severity. The sodium level showed a decreasing trend with worsening ACLF. Clinical severity scores, including the Child-Pugh score, Model for End-Stage Liver Disease score, Model for End-Stage Liver Disease-Sodium score, and CLIF-SOFA score, increased as the ACLF grade increased.

Regarding initial organ failure defined by EASL-CLIF criteria (Supplementary Table 1), 35.7% had initial liver failure (bilirubin ≥12 mg/dL), 23.6% had initial brain failure (hepatic encephalopathy grade 3–4), and 27.1% had initial coagulation failure (INR ≥2.5). Overall, liver failure as defined in this study (including bilirubin ≥12 mg/dL, hepatic encephalopathy grade 3–4, or INR ≥2.5) was present in 61.1% of the population. Additionally, 49.9% had initial renal failure (creatinine ≥2.0 mg/dL), 18.0% required vasopressors for circulatory support, and 31.0% had respiratory failure (PaO_2/FiO_2 ≤200 or SpO_2/FiO_2 ≤214).

Table 1. Baseline Characteristics of the Study Population

Characteristic	ACLF grade				Total (n=339)
	0 (n=35)	1 (n=154)	2 (n=94)	3 (n=56)	
Age, yr	56.23±11.90	57.76±9.53	52.11±11.65	49.79±10.49	54.72±11.00
Male sex	25 (71.43)	120 (77.92)	75 (79.79)	37 (66.07)	257 (75.81)
Systolic blood pressure, mm Hg	124.69±22.88	115.16±27.60	112.85±24.00	101.65±28.61	113.30±26.94
Diastolic blood pressure, mm Hg	75.97±16.35	68.58±16.64	66.38±14.56	60.69±19.34	67.45±16.94
Mean blood pressure, mm Hg	92.21±17.38	84.11±19.49	81.87±16.67	74.35±21.68	82.74±19.41
Respiratory rate, breaths/min	20.31±2.58	19.83±3.10	20.23±2.46	21.50±4.90	20.27±3.30
White blood cell, $\times10^3$/μL	8,661±6,843	9,134±5,228	10,885±6,342	13,082±7,962	10,223±6,382
Hemoglobin, g/dL	11.01±2.43	9.63±2.43	9.58±2.56	9.69±3.07	9.77±2.60
Platelet, $\times10^3$/μL	115.11±84.47	114.12±73.20	102.61±78.35	90.32±53.69	107.10±73.37
Albumin, g/dL	2.78±0.47	2.72±0.65	2.51±0.57	2.55±0.62	2.64±0.61
Total bilirubin, mg/dL	11.53±9.84	5.54±6.86	16.13±11.71	15.53±10.82	10.75±10.59
ALT, U/L	133±311	88±307	146±590	258±499	137±438
AST, U/L	246±485	184±754	472±2,082	712±1,418	357±1,356
PT INR	1.82±0.42	1.64±0.53	2.20±0.78	3.33±2.34	2.09±1.25
Creatinine, mg/dL	0.95±0.35	2.67±2.39	2.10±1.36	2.59±1.45	2.32±1.93
Sodium, mmol/L	132.45±5.53	133.77±6.45	131.93±7.67	131.72±7.43	132.78±6.93
Child-Pugh score	10.43±1.50	9.47±2.18	11.20±1.74	12.46±1.51	10.55±2.20
MELD	21.45±5.37	23.74±6.15	29.29±6.56	35.57±7.99	27.00±8.00
MELD-Na	24.71±5.88	26.07±6.18	31.09±5.99	36.16±6.69	28.99±7.31
CLIF-SOFA score	6.86±2.06	7.29±2.34	10.07±1.77	14.50±3.00	9.21±3.51

Data are presented as mean±SD or number (%).

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease-Sodium; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment.

2. Timing of liver failure

When the study population was divided into three groups—those without liver failure, those who initially showed liver failure, and those who developed liver failure during the course of their illness—we observed that the group without liver failure had significantly better survival rates than the group with liver failure (log-rank p<0.001; adjusted hazard ratio [aHR], 3.6; 95% confidence interval [CI], 1.39 to 9.31, p=0.008 compared with initial liver failure; aHR, 5.7; 95% CI, 1.95 to 16.88; p=0.002 compared with development of liver failure). However, among the patients with liver failure, there were no significant differences in survival rates based on the timing of the liver failure occurrence (log-rank p=0.906; aHR, 1.6; 95% CI, 0.80 to 3.17; p=0.186) (Fig. 1). When the diagnostic threshold for liver failure was lowered, the trend in short-term survival rates based on the timing of liver dysfunction remained similar (Supplementary Fig. 2). The prognosis was favorable when liver dysfunction did not occur, and there were no significant differences in prognosis according to whether liver dysfunction occurred initially or during the course of the illness (log-rank p=0.426).

3. Timing of renal failure

Fig. 2 shows the short-term survival rates based on the timing of renal failure occurrence. The patients were categorized into three groups: those without renal failure, those who had renal failure initially, and those who developed renal failure during the course of their illness. Unlike in the analysis of liver failure, no significant difference in 28-day survival was seen between patients who did not have renal failure and those who had it from the outset (aHR, 0.8; 95% CI, 0.51 to 1.4; p=0.508). However, patients who developed renal failure during the course of their illness exhibited significantly lower survival rates than both those without renal failure (log-rank p=0.021) and those with initial renal failure (log-rank p=0.003). This trend persisted in the multivariate analysis, which showed significantly lower survival rates in patients who developed renal failure than in those with initial renal failure (aHR, 2.3; 95% CI, 1.17 to 4.33; p=0.015).

When the diagnostic threshold for renal failure was lowered, the trend in short-term survival rates based on the timing of renal dysfunction occurrence remained similar (Supplementary Fig. 3). Patients who did not have renal dysfunction and those who had it from the outset showed

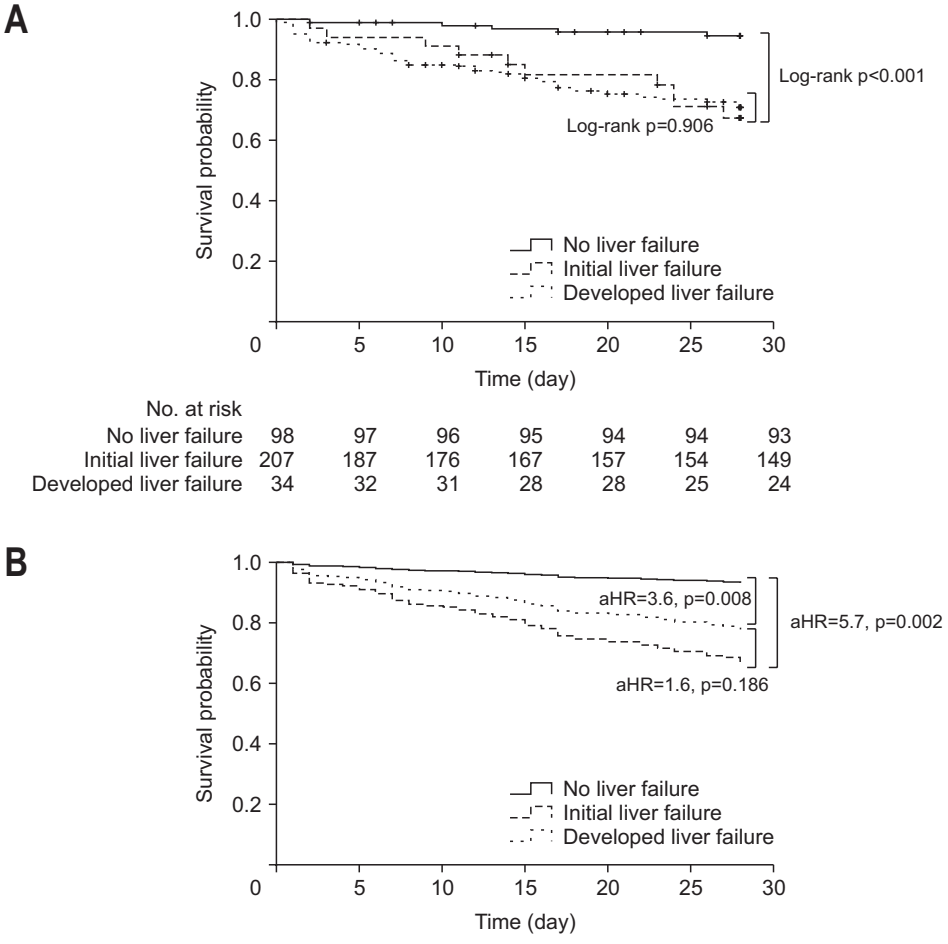

Fig. 1. Survival probability according to time of liver failure. (A) Kaplan-Meier curve showing the survival probability over time for patients with no liver failure, initial liver failure, and developed liver failure. Log-rank p-values are indicated. (B) Survival probability adjusted for age and CLIF-SOFA score, with adjusted hazard ratios (aHR) and p-values indicated for comparisons between no liver failure, initial liver failure, and developed liver failure. CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment.

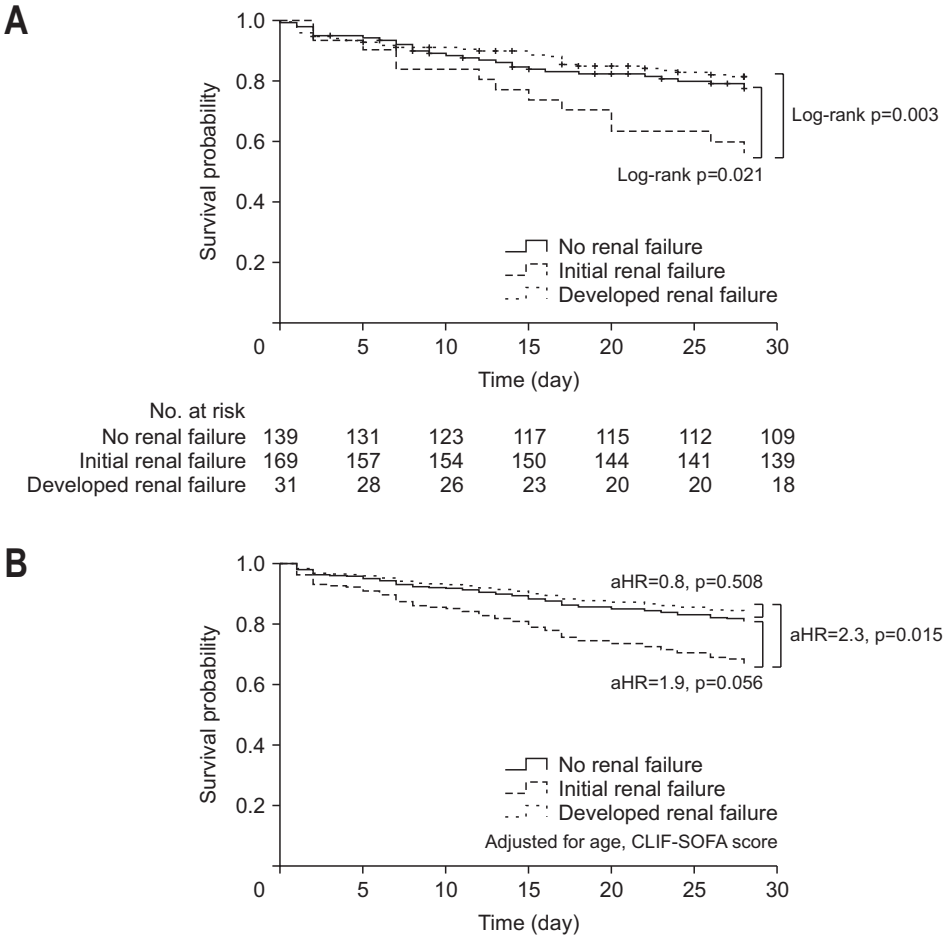

Fig. 2. Survival probability according to time of renal failure. (A) Kaplan-Meier curve showing the survival probability over time for patients with no renal failure, initial renal failure, and developed renal failure. Log-rank p-values are indicated. (B) Survival probability adjusted for age and CLIF-SOFA score, with adjusted hazard ratios (aHR) and p-values indicated for comparisons between no renal failure, initial renal failure, and developed renal failure. CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment.

no significant difference in survival rates. However, patients who developed renal dysfunction during the course of their illness exhibited significantly lower survival rates (log-rank p<0.001).

4. Initial type of organ failure

When analyzing the 28-day survival probability according to the type of initial organ failure, there was a significant difference in survival rates between patients with initial renal failure and those with initial liver failure (log-rank p<0.001) (Fig. 3), indicating a better prognosis for those with initial renal failure. Patients with both liver and renal failure exhibited the poorest survival outcomes, although the difference from initial liver failure alone was not statistically significant (log-rank p=0.111). After adjustment for baseline variables, initial liver failure (aHR, 2.42; 95% CI, 1.04 to 5.62; p=0.040) and combined liver and renal failure (aHR, 2.53; 95% CI, 1.01 to 6.33; p=0.048) were significantly associated with reduced survival compared with initial renal failure (Table 2). There was a consistent lack of a significant difference in survival rates between patients with liver failure and those with combined liver and renal failure (aHR, 1.04; 95% CI, 0.61 to 1.80; p=0.880).

When the threshold for organ failure was lowered to indicate organ dysfunction, the trend in survival probability according to the type of initial organ failure remained consistent with that observed with the higher threshold (Supplementary Fig. 4). Patients with initial renal dysfunction demonstrated a favorable short-term survival rate, significantly higher than that in patients with initial hepatic dysfunction (log-rank p=0.009). There was no statistically significant difference in survival rates between patients with initial hepatic dysfunction and those with initial hepatic and renal dysfunction combined (log-rank p=0.117).

5. Organ failure sequence

To compare short-term survival rates based on the sequence of liver failure and renal failure, the study population was divided into five groups: those who initially manifested renal failure alone, those who initially manifested liver failure alone, those who initially had both liver and renal failure, those who initially had liver failure and later developed renal failure, and those who initially had renal failure and later developed liver failure. As shown in Fig. 4, liver or renal

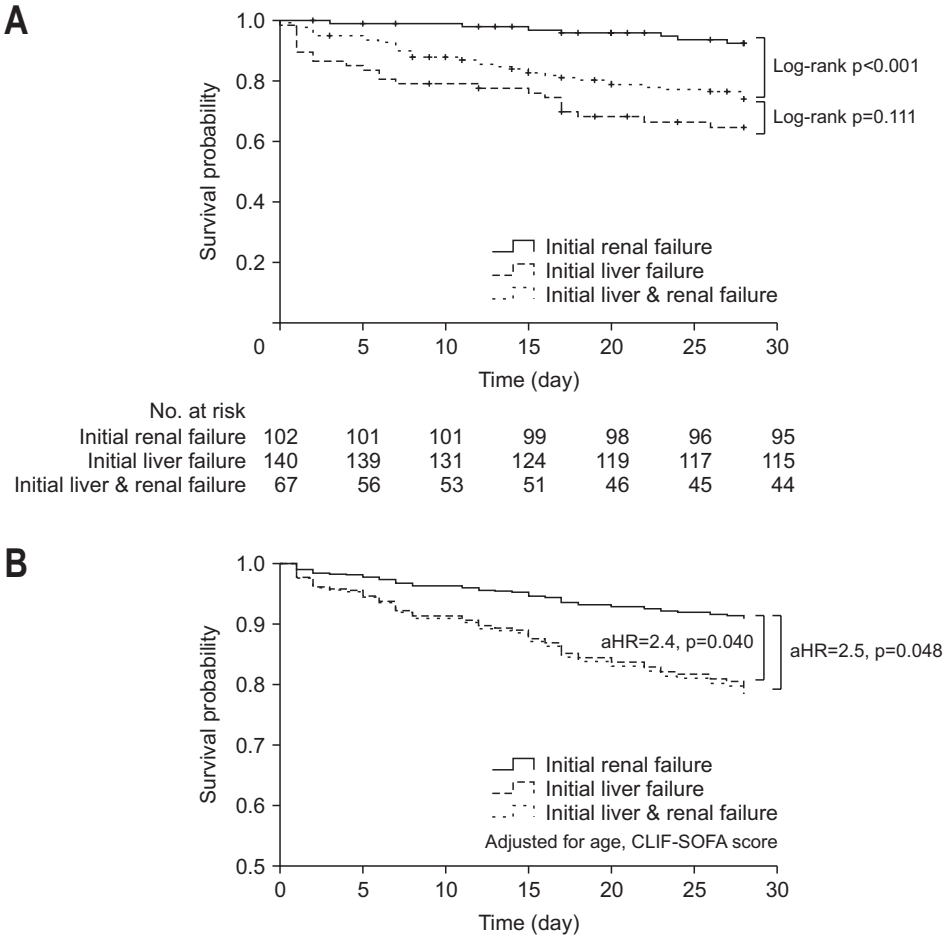

Fig. 3. Survival probability according to initial type of organ failure. (A) Kaplan-Meier curve showing the survival probability over time for patients with initial liver failure, initial renal failure, and initial liver and renal failure. Log-rank p-values are indicated. (B) Survival probability adjusted for age and CLIF-SOFA score, with adjusted hazard ratios (aHR) and p-values indicated for comparisons between initial liver failure, initial renal failure, and initial liver and renal failure. CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment.

Table 2. Survival Outcomes Based on Type of Initial Organ Failure

Type of initial organ failure	28-day survival rate (%)	Adjusted HR (95% CI)	p-value
Initial renal failure	93.1	Ref.	Ref.
Initial liver failure	82.1	2.42 (1.04–5.62)	0.040
Initial liver & renal failure	65.7	2.53 (1.01–6.33)	0.048

HR, hazard ratio; CI, confidence interval; Ref., reference.

failure that developed during hospitalization was more likely to be fatal than liver or renal failure that manifested initially. By contrast, patients who initially manifested renal failure alone had a good prognosis, with a 28-day survival rate of >90%. The group with initial renal failure alone showed a significantly higher survival rate than the group with initial liver failure alone (log-rank p<0.001) or with both liver and renal failure (log-rank p<0.001). The multivariate analysis revealed that patients who presented with renal failure alone had a 12-fold higher survival rate than patients who presented with liver failure alone (aHR, 0.08; 95% CI, 0.01 to 0.63; p=0.016) (Supplementary Table 2). When liver failure and renal failure occurred sequentially, the prognosis was notably unfavorable, with no significant differences in survival rates based on the order of organ failure occurrence (log-rank p=0.438).

When the threshold for organ failure was lowered to indicate organ dysfunction, the trend in survival probability according to the sequence of organ dysfunction remained consistent with that observed with the higher threshold (Supplementary Fig. 5). The group with initial renal dysfunction alone showed a significantly higher survival rate than the group with initial liver dysfunction alone (log-rank p=0.019) or with both liver and renal dysfunction (log-rank p=0.008). When liver dysfunction and renal dysfunction occurred sequentially, patients who initially had liver dysfunction and later developed renal dysfunction showed significantly lower survival rates than patients who initially had renal dysfunction and then developed liver dysfunction (log-rank p=0.004).

DISCUSSION

This study investigated the sequence and impact of organ failure, particularly liver and renal failure, on the short-term survival of patients with ACLF. The findings indicate that

ACLF presenting with initial liver failure has a worse prognosis than ACLF presenting with initial renal failure. Organ failure that develops during the course of illness is more fatal than organ failure that manifests initially. Specifically, ACLF with initial renal failure alone exhibits a favorable prognosis, with a 28-day survival rate exceeding 90%, whereas the prognosis is poor if renal failure develops during the course of the illness. These results emphasize the critical impor-

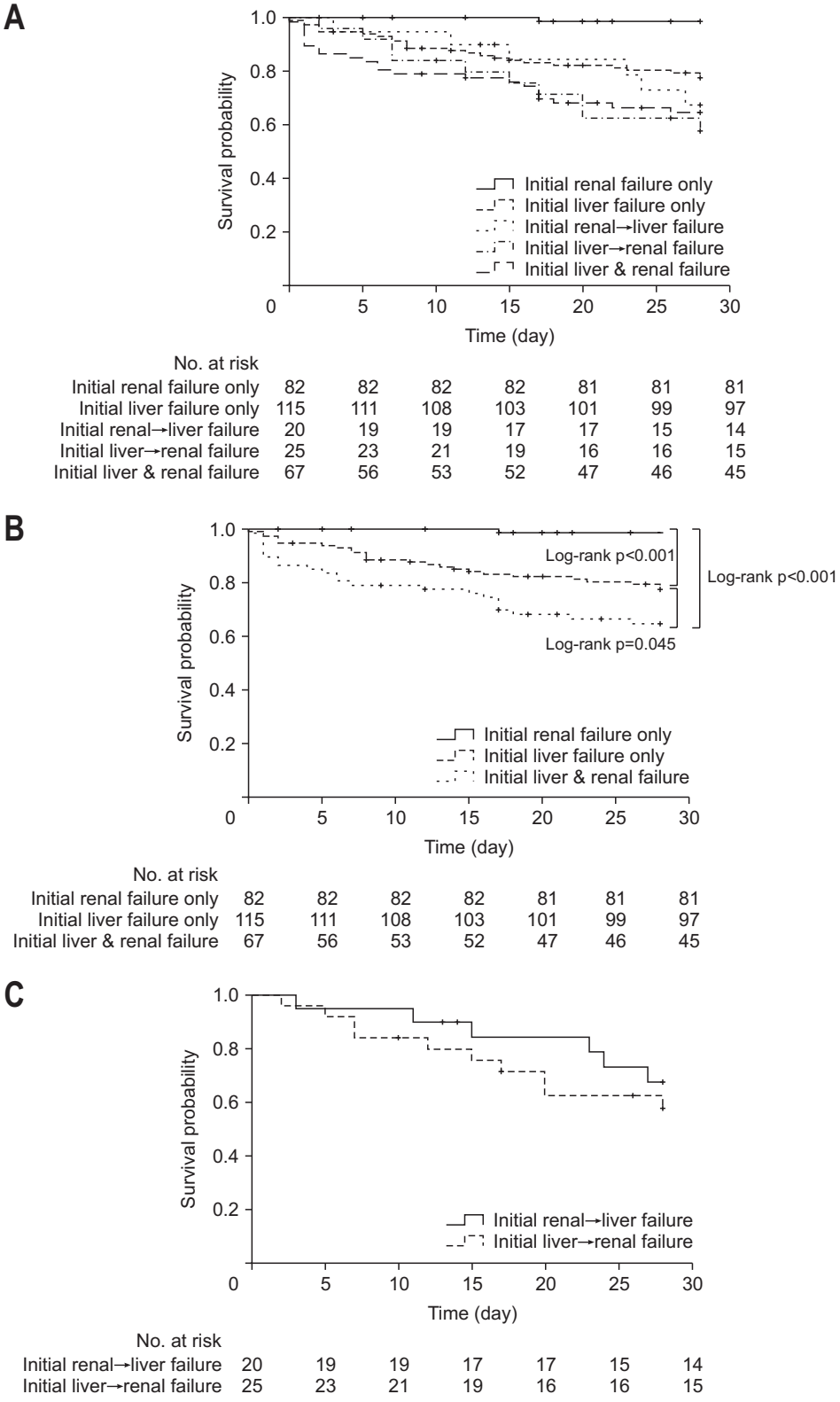

Fig. 4. Survival probability according to organ failure sequence. (A) Kaplan-Meier curve showing the survival probability over time for patients with initial liver failure only, initial liver failure followed by renal failure, initial renal failure only, initial renal failure followed by liver failure, and initial liver and renal failure. (B) Kaplan-Meier curve showing the survival probability over time for patients with initial liver failure only, initial renal failure only, and initial liver and renal failure. Log-rank p-values are indicated. (C) Kaplan-Meier curve showing the survival probability over time for patients with initial liver failure followed by renal failure, and initial renal failure followed by liver failure. Log-rank p-values are indicated. (D) Survival probability adjusted for age and CLIF-SOFA score, with adjusted hazard ratios (aHR) and p-values indicated for comparisons between initial liver failure only, initial liver failure followed by renal failure, initial renal failure only, initial renal failure followed by liver failure, and initial liver and renal failure. CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment.

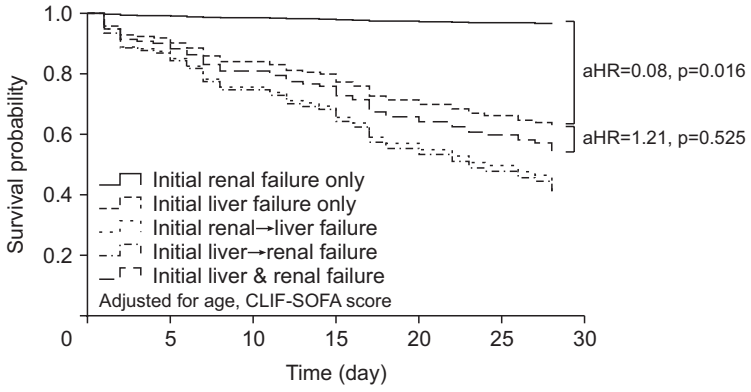

Fig. 4. Continued.

tance of early detection and management of organ failure to improve survival outcomes in patients with ACLF.[6]

Earlier studies have predominantly focused on the presence and number of organ failures in patients with ACLF. It has been established that multiple organ failures are correlated with increased mortality in patients with ACLF, underscoring the severity of the condition.[7-9] However, these studies did not investigate how the timing and sequence of the organ failures might affect the prognosis. Our findings on how liver and renal failure affect ACLF differently, especially in terms of timing, offer new perspectives on the prognosis of ACLF. The observation that initial liver failure leads to poorer outcomes aligns with the finding that the liver's central role in metabolism significantly influences ACLF severity.[2,10,11] Moreover, the detrimental impact of renal failure developing during hospitalization underscores the dynamic and severe nature of ACLF, supporting findings from previous studies that emphasize the critical role of timely intervention.[5,7] The present study suggests that using a lower threshold for diagnosing organ failure does not substantially alter the disease progression or prognosis compared with using a higher threshold. This finding indicates that employing a more sensitive diagnostic threshold could facilitate earlier detection and management of ACLF, potentially improving patient outcomes by preventing the progression of organ failure.[12]

Liver failure is a critical contributor to severe systemic inflammation, which induces mitochondrial dysfunction and exacerbates multiple organ failure.[13] The liver's central role in detoxification and metabolism means that its failure results in the accumulation of toxins and metabolites, adversely impacting various organ systems.[14] Furthermore, liver failure leads to hemodynamic instability characterized by portal hypertension and reduced systemic vascular resistance, which complicates renal perfusion and function.[15] The liver's role in immune regulation is also significant; its failure causes immune dysregulation, increasing patient susceptibility to infections, a major cause of mortality in ACLF.[16] Typically, liver failure is the initial type of organ failure in ACLF, triggering a cascade of subsequent organ failures, including renal failure. By contrast, patients who initially present with renal failure in the absence of liver failure tend to show a more favorable short-term prognosis. This may be explained by the greater reversibility of renal dysfunction, which often results from hemodynamic alterations, volume status changes, or nephrotoxic insults that can improve with timely management. Moreover, preserved liver function in this group allows maintenance of detoxification, metabolic, and immune-regulatory functions, thereby preventing the vicious cycle of systemic inflammation and multiorgan dysfunction.

Despite ongoing demands for a unified definition of ACLF, a solid consensus has yet to be established. The discrepancy in diagnostic criteria, particularly between European and Asian countries, underscores the complexity and variability of this disease entity.[6,17] The main difference between the two representative definitions is that in the APASL definition, liver failure is the primary driver of severity,[10] while in the EASL-CLIF definition, the driver is not necessarily the liver failure, rather, renal failure is mandatory for diagnosis. In the EASL-CLIF context, ACLF can be diagnosed even in the absence of liver failure if renal failure is present. However, as shown in this study, patients with renal failure only showed a significantly lower likelihood of short-term mortality than patients with typical ACLF, raising concerns about whether such cases should be considered true ACLF. Some of these patients may have experienced transient acute kidney injury triggered by infection or bleeding, which resolved without progression to further organ failures. In addition, because the EASL-CLIF definition does not provide specific modifications for patients with chronic kidney disease, cirrhotic patients with preexisting chronic kidney disease can fulfill the renal failure criterion based solely on serum creatinine levels (≥2.0 mg/dL). Since renal failure was the most frequent organ failure in the CANONIC study (55.8% of ACLF cases),[7] this limitation is particularly rele-

vant. Patients meeting only the renal failure criterion exhibit a higher survival rate, suggesting a fundamentally different prognosis and potentially less severe condition than traditional ACLF cases involving liver failure. Furthermore, the EASL-CLIF criteria for diagnosing liver failure are generally more stringent than the APASL standards. The APASL criteria have a lower threshold for liver failure and do not require multiple organ failure, which might facilitate earlier detection and management of ACLF.[18] Our study demonstrated that patient groups diagnosed using lower threshold criteria exhibited a similar prognosis based on the specific pattern of organ failure or the sequence of organ failure manifestations. This indicates that the unique characteristics of ACLF persist even with these lower diagnostic thresholds. Adopting lower thresholds could be advantageous by allowing for more timely intervention, potentially improving patient outcomes.[19-21]

Our findings have important clinical implications for ACLF management. The markedly favorable prognosis of patients with isolated renal failure (28-day survival >90%) compared to those with initial liver failure challenges the current approach of treating all single organ failures equally within ACLF grading systems, suggesting that organ failure type should be incorporated into risk stratification models. The significantly worse outcomes associated with sequential organ failure development during hospitalization, regardless of order, underscores the critical importance of preventing secondary organ failure. This indicates that patients with single organ failure at admission require intensive monitoring and aggressive preventive measures tailored to their specific organ failure pattern—those with initial liver failure need renal protective strategies, while those with initial renal failure warrant close monitoring for hepatic decompensation. From a resource utilization perspective, patients with isolated renal failure might be managed in intermediate care settings with appropriate monitoring, while those with initial liver failure or at high risk for sequential organ failure may require immediate intensive care support. These findings suggest that risk stratification in ACLF should incorporate not only ACLF grade but also the initial organ failure type to enable more personalized and effective management strategies.

The strengths of this study include its use of a large, well-defined patient population from the pKACLiF cohort, which enhances the reliability and generalizability of the findings. The results of this study can be attributed to the complex pathophysiology of ACLF. Initial liver failure may trigger a cascade of metabolic and hemodynamic disturbances, exacerbating overall clinical deterioration and leading to poor outcomes.[13,22] Conversely, renal failure might be more manageable initially but can rapidly worsen if not addressed promptly. The finding that organ failure developing during hospitalization is more likely to be fatal highlights the need for vigilant monitoring and timely interventions.

This study had several limitations that should be acknowledged. First, the observational nature of the study precludes establishing causality. Second, the cohort comprised only Korean patients, which may affect the generalizability of the findings to other populations. Nonetheless, the study's large sample size and detailed methodology mitigate this concern. Third, our analysis focused primarily on the prognostic significance of organ failure types and sequences, rather than comprehensively evaluating potential modifying factors such as precipitating factors and treatment-related variables. While these factors undoubtedly influence ACLF outcomes, we postulated that the pattern of organ failure manifestation itself incorporates much of the prognostic impact, as they are ultimately reflected in the dynamics of organ failure development and resolution. Our longitudinal assessment of organ failure dynamics likely encompasses the clinical impact of various precipitants and their treatment responses. Nonetheless, we acknowledge that future studies incorporating a more detailed analysis of precipitating factors and therapeutic interventions would provide broader insights and help refine risk stratification in ACLF. Well-designed, prospective, and multinational studies are warranted to achieve a more comprehensive understanding of ACLF, clarify discrepancies in diagnostic criteria, and improve patient management strategies.

In conclusion, ACLF presenting with initial renal failure demonstrates a more favorable prognosis than ACLF presenting with initial liver failure, and organ failure that develops during the course of illness is more fatal than organ failure that manifests initially. When ACLF is characterized by initial renal failure alone, it exhibits a good prognosis with a 28-day survival rate exceeding 90%. Because using a higher threshold for the diagnosis of organ failure may result in overlooking patients with ACLF who have similar outcomes, considering a lower threshold for diagnosis may be warranted.

CONFLICTS OF INTEREST

W.K. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.Y.J., Y.C. Data analysis and interpretation: Y.C. Drafting of the manuscript: Y.C. Critical revision of the manuscript for important intellectual content: J.Y.J., S.W.J., D.S.S., H.Y.K., Y.K.J., T.H.K., H.J.Y., E.L.Y., K.T.S., J.J.Y., S.G.K., M.Y.K., S.E.K., J.H.K., J.G.P., W.K., D.J.K. Statistical analysis: Y.C. Obtained funding: Y.C. Study supervision: J.Y.J. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl250299.

DATA AVAILABILITY STATEMENT

Data analyzed in this study are available from the corresponding author upon reasonable request.

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