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Outcomes of critically ill patients with liver failure who require mechanical ventilation: A retrospective, single-center study

Atsuyoshi Mita | Sari Shimizu | Takashi Ichiyama | Takateru Yamamoto | Akinori Yamaguchi | Kosuke Sonoda | Kotaro Mori | Tomokatsu Yamada | Hiroyuki Nakamura | Hiroshi Imamura

Intensive Care Unit, Shinshu University Hospital, Shinshu University School of Medicine, Matsumoto, Japan

Correspondence
Atsuyoshi Mita, Intensive Care Unit, Shinshu University Hospital, Shinshu University School of Medicine, 3-1-1 Asahi, 390-8621 Matsumoto, Japan.
Email: mita@shinshu-u.ac.jp

Abstract

Background and Aims: Critically ill patients with liver failure have high mortality. Besides the management of organ-specific complications, liver transplantation constitutes a definitive treatment. However, clinicians may hesitate to introduce mechanical ventilation for patients on liver transplantation waitlists because of poor prognosis. This study investigated the outcomes of intensive care and ventilation support therapy effects in patients with liver failure.

Methods: This single-center study retrospectively enrolled 32 consecutive patients with liver failure who were admitted to the intensive care unit from January 2014 to December 2020. The medical records were reviewed and analyzed retrospectively for Acute Physiologic and Chronic Health Evaluation (APACHE)-II. The model for end-stage liver disease scores, 90-day mortality, and survival was assessed using the Kaplan–Meier method.

Results: The average patient age was 45.5 ± 20.1 years, and 53% of patients were women. On intensive care unit admission, APACHE-II and model for end-stage liver disease scores were 20 and 28, respectively. Among 13 patients considered for liver transplantation, 4 received transplants. Thirteen patients (40.6%) were intubated and mechanically ventilated in the intensive care unit. The 90-day mortality rate of patients with and without mechanical ventilation in the intensive care unit (13, 61.5% vs. 19, 47.4%, $p = 0.4905$) was similar. APACHE-II score >21 was an independent predictor of mechanical ventilation requirement in patients with liver failure during intensive care unit stay.

Conclusion: Although critically ill patients with liver failure are at risk of multiorgan failure with poor outcomes, mechanical ventilation did not negatively affect the 90-day mortality or performance rates of liver transplantation. Clinicians should consider mechanical ventilation-based life support in critically ill patients with liver failure who are awaiting liver transplantation.

KEYWORDS
liver transplantation, liver failure, liver cirrhosis, mechanical ventilation, respiratory support, intensive care

1 | INTRODUCTION

Critically ill patients with liver failure (LF) have a very high mortality risk.[1] Acute liver failure (ALF; also called fulminant hepatic failure) requires intensive care, including artificial and bioartificial therapies, because of high-grade encephalopathy and multiorgan dysfunction. Patients with acute and subacute types have survival rates of 49.2% and 20.7%, respectively.[2,3] Liver cirrhosis may result in complications, including gastrointestinal bleeding, sepsis, or renal failure, that frequently necessitate intensive care unit (ICU) admission[4] and that are associated with low survival rates (59%–63% in the ICU and 46%–51% in the hospital).[5,6] Strategies to manage organ-associated complications in general critical illnesses may not be appropriate for patients with LF, for whom the definitive treatment is frequently liver transplantation.[1] Although the mortality rate is much higher among patients with LF who need ICU admission,[7] these patients constitute only a small proportion of ICU admissions.[8] As the clinical course varies among patients based on acute, acute-on-chronic, and late-onset LFs, the selection of an optimal management strategy is often difficult in severe cases, especially with regard to clinical decision-making on how and when to escalate or withdraw therapy. Patients who require organ-specific support, such as mechanical ventilation, have higher mortality risks,[8,9] and mechanically ventilated patients with cirrhosis often progress to multiorgan failure,[10] which results in poor prognosis.[6] Therefore, respiratory complications might be a major reason for the hesitation of clinicians to place mechanically ventilated patients on waiting lists for liver transplantation.[2] However, the appropriate management of respiratory complications in patients with severe LF remains obscure, although there are reports in the literature regarding possible clinical management options.[2,11–18]

This study was conducted with an aim to evaluate the management and treatment outcomes of patients with LF, especially those who needed mechanical ventilation therapy and are admitted to the general ICU.

Key points

What's known

As critically ill patients with liver failure have high mortality, clinicians hesitate to introduce mechanical ventilation for patients on liver-transplantation waitlists because of the poor prognosis.

What's new

We aimed to clarify the management and treatment outcomes of patients with liver failure, especially those who needed mechanical ventilation.

What the clinical implications of this study are

Mechanical ventilation-based life support is not an adverse prognostic factor for critically ill patients with liver failure who are on a waitlist for liver transplantation. Therefore, clinicians should unhesitatingly provide mechanical ventilation-based life support in this patient group.

2 | METHODS

2.1 | Study design

This single-center, retrospective cohort study was conducted at a university hospital in Japan.

2.2 | Patients

Among 5842 ICU admissions, this study included conse+cutive patients diagnosed with LF for ICU admission at Shinshu University Hospital, Matsumoto, Japan, between January 2014 and December 2020. LF included ALF, late-onset hepatic failure (LOHF), acute-on-chronic liver failure (ACLF), and chronic liver failure (CLF). Patients admitted to the ICU for postoperative care immediately after liver transplantation were excluded from this study.

ALF was defined as Grade ≥II severe hepatic encephalopathy (according to the Inuyama Symposium Criteria) that developed within 8 weeks from symptom onset along with a prothrombin time <40% of the standardized value.[19] LOHF was defined as severe hepatic encephalopathy that developed between 8 and 24 weeks of disease onset.[19] ACLF was defined as acute decompensated cirrhosis associated with organ failures and severity that was evaluated using the European Association for the Study of the Liver-CLF score.[17] CLF was included as another status, such as decompensated liver cirrhosis.

2.3 | Assessment methods

Patients' medical records were retrospectively reviewed and analyzed. Acute Physiologic and Chronic Health Evaluation (APACHE)-II,[20] APACHE-III,[21] Simplified Acute Physiology Score (SAPS)-II,[22] Sequential Organ Failure Assessment (SOFA),[23] Child–Pugh classification,[24] model for end-stage liver disease

(MELD),[25] and Glasgow Coma Scale (GCS)[26] scores were calculated as reported previously. To evaluate optimal management for respiratory complications, we separated patients with LF into two groups: patients requiring intubation for invasive mechanical ventilation (V group) and patients not requiring intubation (no-V group) during ICU stay. Patient characteristics, illness severity assessed by scoring systems, treatments, and outcomes were evaluated. The primary outcome was the 90-day mortality rate post-ICU admission.

2.4 | Ethics declarations

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shinshu University (registration number: 5449). According to the guidelines on research performed using patient data at Shinshu University, the requirement of informed consent was waived, and the relevant information was provided to patients and their families before their inclusion in the study.

2.5 | Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) for normal distribution or as median (interquartile range) for non-normal distribution. Categorical variables are presented as proportions. The participants' characteristics were compared using the Student's *t*-test or Mann–Whitney *U* test for continuous variables and by the chi-square or Fisher's exact test for categorical variables.

Logistic regression was performed to identify individual predictor score systems for intubation in the ICU. Factors associated with invasive mechanical ventilation in the univariate analysis were included in the multivariate analysis. Continuous variables were transformed into categorical variables through cut-off values analyzed using receiver operating characteristic (ROC) curve analysis for APACHE-II and SAPS-II.[27] After ROC curve values were calculated and plotted, cut-off values were identified to magnify sensitivity and specificity using the area under the curve. Subsequently, multivariate logistic regression analysis was performed to identify the independent predictor for intubation in the ICU between APACHE-II and SAPS-II scores.

Survival rates and ventilation-free rates were analyzed using the Kaplan–Meier method with the Cox's proportional hazards model after ICU admission, and the difference was evaluated using a log-rank test. Survival time was defined as the days between ICU admission and events such as death and intubation. Liver transplantation was considered a censor.

All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with JMP, version 15 (SAS Institute).

3 | RESULTS

A total of 64 (1.1%) patients met the eligibility criteria. Overall, 50% ($n = 32$) of the patients who were admitted immediately after liver transplantation for postoperative care were excluded, and finally, data of 32 patients were analyzed. The mean age of the patients at ICU admission was 45.5 ± 20.1 years, and 53.1% of the patients were women (Table 1). The primary liver diseases included diagnosed cholestatic liver diseases in 6 patients (18.8%, including 3 cases of primary sclerotic cholangitis, 2 of biliary cirrhosis, and 1 of primary biliary cholangitis); hepatocellular liver diseases in 21 (65.7%, including 6 cases of cryptogenic hepatitis, 5 of alcoholic steatohepatitis, 4 of drug-induced hepatitis, 3 of hepatitis C, 2 of nonalcoholic steatohepatitis, and 1 of autoimmune hepatitis); metabolic liver diseases in 3 (9.4%, including 1 case each of Wilson disease, porphyria, and congenital disorders of glycosylation type 2); and other conditions in 2 (6.3%, including post-transplant graft failure and post-hepatectomy sepsis). Furthermore, 19 patients were transferred from general wards after a median of 15 (5–36) days of treatment. The remaining 13 patients were directly admitted to the ICU from other hospitals or the emergency room. Twelve patients (32.3%) had ALF, 2 (6.3%) had LOHF, and 18 (56.3%) had CLF (Table 1). Among the 18 patients with CLF, 10 satisfied the criteria for ACLF on ICU admission as follows: complicated renal failure in 9 patients; hepatic encephalopathy in 2 patients; and coagulopathy, heart failure, and respiratory failure in 1 patient each. The APACHE-II, APACHE-III, Child–Pugh, SAPS-II, and SOFA scores of the 32 patients who were admitted to the ICU were 20.1 ± 10.3, 83.5 ± 28.3, 12.2 ± 3.7, 39.6 ± 21.5, and 8.9 ± 3.3 points, respectively. The median MELD score for the same patient group was 27 (interquartile range, 21–36) points (Table 1).

Complications present on ICU admission included infection in 21 (65.6%) patients, variceal bleeding in 3 (9.4%), hepatic encephalopathy in 19 (59.4%), respiratory failure in 4 (12.5%), and renal failure in 18 (56.3%) (Table 1).

3.1 | Invasive mechanical ventilation

Overall, 13 patients (40.6%) were intubated and mechanically ventilated in the ICU (Supporting information 1, V group); the reasons for mechanical ventilation included hepatic encephalopathy in three patients, pneumonia-related complications in three, septic shock in two, lung edema in one, hydrothorax in one, continuous renal replacement therapy (CRRT) in one, CO_2 narcosis in one, and hypovolemic shock in one. Noninvasive positive pulmonary ventilation (NPPV) was introduced in four patients during ICU stay, and three of these patients were subsequently intubated and received invasive mechanical ventilation for respiratory failure (Supporting information 1); however, one patient was maintained successfully by NPPV only until liver transplantation. The median duration between intubation and ICU admission was 4 (0–12) days.

TABLE 1 Participant characteristics in this study.

Variable	All patients $n = 32$	Ventilation $n = 13$	No-ventilation $n = 19$	p-value
Age on admission (years), mean ± SD	45.5 ± 20.1	44.3 ± 5.7	46.2 ± 4.7	0.83
Pediatrics,[a] *n* (%)	3 (9.3)	2 (15.4)	1 (5.3)	0.34
Female sex, *n* (%)	17 (53.1)	7 (53.9)	10 (52.6)	0.95
Body mass index (kg/m^2)	24.6 ± 5.9	23.9 ± 5.3	25.1 ± 6.4	0.59
Primary liver diseases, *n* (%)				0.09
Cholestatic disease	6 (18.8)	3 (23.1)	3 (15.8)	
Hepatocellular disease	21 (65.4)	7 (53.9)	14 (73.3)	
Metabolic disease	3 (9.4)	2 (15.4)	1 (5.3)	
Others	2 (6.3)	1 (7.7)	1 (5.3)	
Types of liver failure, *n* (%)				0.08
Acute	12 (37.5)	8 (61.5)	4 (21.1)	
Late onset	2 (6.3)	0 (0.0)	2 (10.5)	
Chronic	5 (15.6)	1 (7.7)	4 (21.1)	
Acute-on-chronic	13 (40.6)	4 (30.8)	9 (47.4)	
APACHE-II score	20.1 ± 10.3	25.1 ± 12.4	16.7 ± 7.2	0.02
APACHE-III score	83.5 ± 28.3	90.7 ± 7.8	78.5 ± 6.4	0.23
Child–Pugh score	12.2 ± 3.7	13.2 ± 5.5	11.5 ± 1.3	0.19
MELD score, (IQR)	27 (21, 36)	29 (21, 36)	26 (21, 35)	0.73
SAPS-II score	39.6 ± 21.5	50.5 ± 26.9	32.2 ± 13.2	0.02
SOFA score at admission	8.9 ± 3.3	10.1 ± 4.1	8.2 ± 2.3	0.12
GCS score, (IQR)	14 (13, 15)	13 (7.5, 14)	15 (14, 15)	0.005
Complication on ICU admission				
Infection, *n* (%)	21 (65.6)	11 (84.6)	10 (52.6)	0.05
Variceal bleeding, *n* (%)	3 (9.4)	2 (15.4)	1 (5.3)	0.34
Hepatic encephalopathy, *n* (%)	19 (59.4)	9 (69.2)	10 (52.6)	0.34
Respiratory failure, *n* (%)	4 (12.5)	4 (30.8)	0 (0.0)	0.005
Renal failure, *n* (%)	18 (56.3)	7 (53.9)	11 (57.9)	0.82
Laboratory findings on ICU admission				
T. Bil, mg/dL, (IQR)	19.1 (4.2, 24.8)	21.5 (14.6, 24.0)	8.5 (3.2, 25.5)	0.27
Ammonia, μg/dL	79.3 ± 48.3	90.8 ± 50.6	71.4 ± 46.4	0.27
Cr, mg/dL, (IQR)	1.3 (0.7, 3.6)	1.2 (0.5, 3.6)	1.7 (0.9, 3.8)	0.19
Albumin, mg/dL	2.5 ± 0.7	2.6 ± 0.8	2.4 ± 0.6	0.46
PT-INR (IQR)	1.9 (1.5, 2.6)	1.9 (1.6, 2.8)	1.8 (1.5, 2.4)	0.33
WBC/mm^3	9,098 ± 6,146	8,207 ± 5416	10,399 ± 7,107	0.21
Platelet, ×10^4/mm^3	10.6 ± 9.5	10.6 ± 9.4	10.6 ± 9.8	0.98

Abbreviations: APACHE, acute physiologic and chronic health evaluation; Cr, creatinine; GCS, Glasgow Coma Scale; IQR, interquartile range; MELD, models of end-stage liver disease; PT-INR, prothrombin time-international normalized ratio; SAPS-II, simplified acute physiology score; SOFA, sequential organ failure assessment; T.Bil, total bilirubin; WBC, white blood cell.

[a]Pediatrics included patients aged <18 years.

At ICU admission, age, sex ratio, and body mass index were comparable between the 13 patients who required invasive mechanical ventilation (V group) and the remaining 19 patients who did not require invasive mechanical ventilation (no-V group) (Table 1). In the V group, four patients (30.8%) experienced respiratory failure due to pneumonia or lung edema at ICU admission. The results of blood gas analyses were similar in both the groups at ICU admission (Table 2). Although liver-specific scores, including Child–Pugh and MELD, did not differ significantly, the APACHE-II and SAPS-II scores were significantly higher in the V group than in the no-V group (Table 1). The SOFA score at ICU admission was comparable between the two groups. Among the 13 patients in the V group, 5 were intubated on the day of ICU admission and 8 received invasive mechanical ventilation 4–31 days after ICU admission. Three of these 8 patients initially underwent induced NPPV (1–14 days) before intubation. The SOFA scores for these 8 patients were significantly worse immediately before intubation than those on the day of ICU admission (9.3 vs. 11.8 points, $p = 0.04$: paired Student's *t*-test; Table 1).

3.2 | Predictors of invasive mechanical ventilation

Logistic regression analysis was performed to identify independent predictors of invasive mechanical ventilation following ICU admission because of LF. The univariate regression analysis showed that the APACHE-II and SAPS-II scores were associated with invasive mechanical ventilation during ICU stay (Table 3). Cut-off values identified using ROC curve analysis were 21 points for APACHE-II and 46 points for SAPS-II (Supporting information 2). APACHE-II score ≥21 was identified as an independent predictor of the need for invasive mechanical ventilation in patients with LF during ICU stay (Table 3). The mechanical ventilation-free rate was significantly higher among patients with <21 points of APACHE-II score than among those who had ≥21 points (30 days: 88.0 vs. 9.9%, 90 days: 75.4 vs. 9.9%, $p < 0.001$; Figure 1).

3.3 | Treatment for liver failure

Critically ill patients with LF stayed in the ICU for a median duration of 11.0 (2.0–26.5) days (Table 4). Treatment for LF (Table 4) included CRRT in 24 patients (75.0%) and drainage for hepatic hydrothorax and/or ascites accumulation in 7 (21.9%). The need for CRRT was higher in the V group than in the no-V group (100.0 vs. 57.9%, $p = 0.01$).

Thirteen patients (40.6%, seven in the V group and six in the no-V group) were considered for liver transplantation and five underwent liver transplantation. Four patients were already actively on the transplant waiting list at ICU admission; however, only one received liver transplantation, whereas the remaining three patients, including one who survived for 172 days after ICU admission, died before receiving a transplant. Among the remaining nine patients considered for liver transplantation after ICU admission, four underwent liver transplantation (two underwent deceased donor liver transplantation and two underwent living donor liver transplantations). The remaining five patients, including one who survived for 92 days after ICU admission, died before receiving a transplant.

Nineteen patients were not considered for liver transplantation, and the reasons included ongoing alcohol use in six patients; complications of kidney disease in four; concurrent malignancy in two; refusal for transplantation in two; and advanced age, pneumonia, pancreatitis, multiorgan failure, and suicidal attempt in one patient each.

3.4 | Mortality

Among the 32 patients, 16 (50.0%) died during ICU stay and 17 (53.1%) died within 90 days after ICU admission. Two patients (16.7%) in the V group developed ventilation-associated pneumonia (VAP) during invasive mechanical ventilation; 1 recovered to extubation while on the liver transplant waiting list; and the other underwent living donor liver transplantation after recovery from VAP during invasive mechanical ventilation (Supporting information 1).

TABLE 2 Arterial blood gas analysis on ICU admission.

	All *n* = 32	Ventilation *n* = 13	No-ventilation *n* = 19	*p*-value
RR, rpm (IQR)	21.0 (16.3, 26.8)	22.0 (17.5, 27.0)	21.0 (16.0, 27.0)	0.56
FiO_2 (IQR)	0.21 (0.21, 0.40)	0.21 (0.21, 0.50)	0.21 (0.21, 0.30)	0.34
$PaCO_2$, Torr	34.3 ± 8.2	36.2 ± 10.3	32.9 ± 6.0	0.28
PaO_2, Torr	107.6 ± 50.8	120.2 ± 67.9	95.0 ± 21.1	0.23
SpO_2, % (IQR)	97.0 (95.7, 99.5)	96.6 (94.1, 98.6)	97.2 (96.0, 98.3)	0.80
Lactate, mg/dL (IQR)	15.0 (11.0, 21.0)	16.0 (11.0, 18.5)	15.0 (13.3, 27.2)	0.54
PaO_2/FiO_2	361.4 ± 108.6	347.2 ± 119.0	375.6 ± 100.4	0.53

Abbreviations: FiO_2, fraction of inspiratory oxygen; IQR, interquartile range; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PaO_2/FiO_2, $PaCO_2$-to-FiO_2 ratio; RR, respiratory rate.

TABLE 3 Analysis to determine predictors of the need for invasive mechanical ventilation in patients with liver failure during ICU stay.

	Univariate analysis				Multivariate analysis	
Variable	**Odds ratio (IQR)**	**Cut-off**	***p*-value**	**Variable**	**Odds ratio (IQR)**	***p*-value**
SOFA score on ICU admission	1.21 (0.95–1.53)		0.11	APACHE-II score ≥21	16.00 (1.22–210.59)	0.02
APACHE-II score	1.11 (1.00–1.22)	21.0	0.02	SAPS-II score ≥46	1.17 (0.07–18.35)	0.91
APACHE-III score	1.02 (0.99–1.04)		0.21			
SAPS-II score	1.05 (1.01–1.11)	46.0	0.01			
Child–Pugh score	1.16 (0.91–1.46)		0.18			
MELD score	1.02 (0.93–1.12)		0.71			

Abbreviations: APACHE, acute physiologic and chronic health evaluation; IQR, interquartile range; MELD, models of end-stage liver disease; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment.

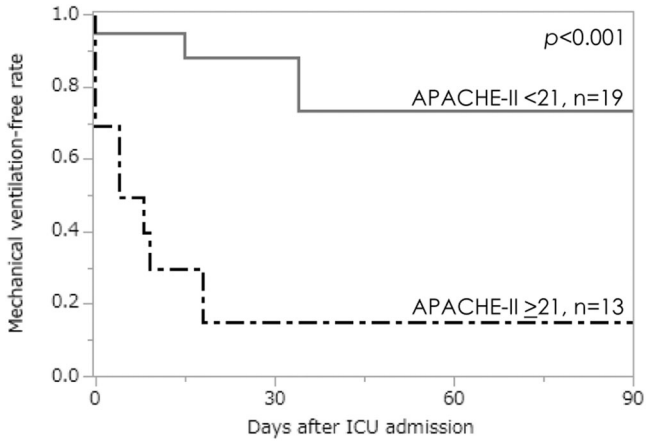

FIGURE 1 Intergroup difference in the mechanical ventilation-free rates after ICU admission between patients with an APACHE-II score ≥ 21 and < 21. After ICU admission, patients with liver failure and an APACHE-II score <21 had a lower mechanical ventilation-free rate than those with an APACHE-II score ≥21. ICU, intensive care unit.

The 90-day mortality rate was comparable between the two groups (61.5 vs. 47.4%, $p = 0.49$), and the performance rate of liver transplantation was similar (23.1 vs. 10.5%) (Table 4). Patient survival rates from the ICU admission day, according to the Kaplan–Meier method, indicated no significant intergroup difference ($p = 0.86$, Figure 2).

4 | DISCUSSION

In this study, patients with LF, such as liver cirrhosis and fulminant hepatic failure, who were admitted to the ICU had low 90-day survival rates owing to multiorgan failure that required organ-specific support. Furthermore, our analysis showed that invasive mechanical ventilation had no effect on survival rates and performance rates of liver transplantation. This finding is consistent with the results mentioned in previous reports, which show that respiratory failure is not a significant prognostic factor in patients with liver cirrhosis[14,28] and ALF,[29] although a few reports have suggested a negative effect of lung injury on outcome in patients with cirrhosis.[15,30] The 90-day mortality rate in this study is similar to that in previous reports, which is 63%–93%.[10] The reasons for requiring intubation included indirect complications associated with original liver diseases, such as pneumonia and septic shock. Therefore, patients could undergo liver transplantation after recovery from those complications by treatment under invasive mechanical ventilation.

Only 1.1% of the patients at our ICU were admitted to be treated for LF. Although our institute has a liver transplantation program, the proportion of admission for patients with LF is very low. This indicates the difficulty in obtaining data on critically ill patients with end-stage liver disease. Mechanically ventilated patients with cirrhosis often progress to multiorgan failure.[10] Liver transplantation is the only curative treatment for patients with severe liver diseases, such as fulminant hepatic failure and decompensated liver cirrhosis. In this study, only 40% of the patients were under consideration for liver transplantation. Patients may be denied consideration for liver transplantation for reasons predating their critical illness since organs are donated to patients most likely to benefit from transplantation.[31] It is crucial to identify which patients are most likely to benefit from transplantation and maintain their condition for liver transplantation. Management to avoid liver function deterioration and complications of other organs, including renal and respiratory failure, is vital for successful liver transplantation.

In this study, pneumonia was identified as the reason for invasive mechanical ventilation and a complication of VAP. Pneumonia was well controlled, and two of five patients successfully underwent liver transplantation. Pneumonia is the most common infection in patients with ALF,[13,32] and causes a complication in 9.8% of patients with cirrhosis who are admitted to the ICU.[33] Treatments such as invasive mechanical ventilation for pneumonia were performed even for critically ill patients with LF.

Hepatic hydrothorax and ascites that accumulate in the context of liver cirrhosis and portal hypertension affect

TABLE 4 Treatment and outcome of patients with liver failure.

	All *n* = 32	Ventilation *n* = 13	No-ventilation *n* = 19	*p*-value
CRRT, *n* (%)	24 (75.0)	13 (100.0)	11 (57.9)	0.01
Drainage,[a] *n* (%)	7 (21.9)	1 (7.7)	6 (31.6)	0.20
Liver transplantation, *n* (%)	5 (15.6)	3 (23.1)	2 (10.5)	0.37
30-day survivor, *n* (%)	19 (59.4)	8 (61.5)	11 (57.9)	>0.99
90-day survivor, *n* (%)	15 (46.9)	5 (38.5)	10 (52.6)	0.49
Survival period, days (IQR)	20.5 (10.3–44.8)	24.0 (11.5–43.5)	19 (7.0–48.0)	0.60
ICU stay, days (IQR)	11.0 (2.0–26.5)	25.0 (8.0–42.0)	7.0 (2.0–13.0)	0.02

Abbreviations: CRRT, continuous renal replacement therapy; IQR, interquartile range.
[a]Drainage of hepatic hydrothorax and/or ascites accumulation.

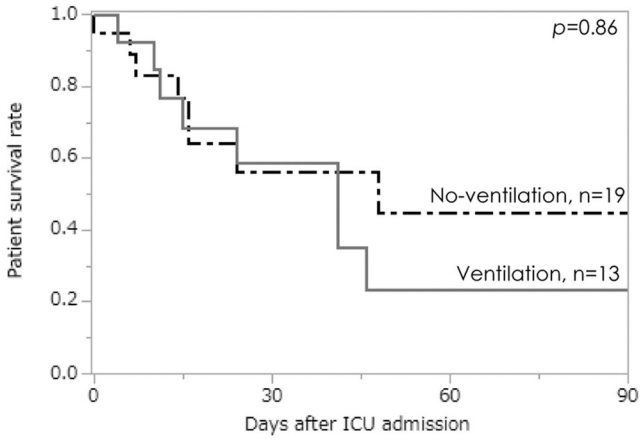

FIGURE 2 Intergroup differences in patient survival rates after ICU admission between the Ventilation and No-ventilation groups. The patient survival rates after ICU admission was comparable between the ventilation and no-ventilation groups. ICU, intensive care unit.

respiratory function. Hepatic hydrothorax develops in 13–15% of patients with liver cirrhosis.[13] Abdominal distention owing to ascites negatively affects respiratory function. Removing pleural effusion and ascites is an important treatment to avoid respiratory failure in patients with liver cirrhosis. The guidelines recommend that ascites >5 L be drained in tandem with albumin administration.[12,34] In this study, 21.9% of the patients with large volumes of pleural effusion and/or ascites were treated by drainage to avoid respiratory failure.

Hepatopulmonary syndrome (HPS) causes an oxygenation defect due to intrapulmonary vascular shunting that develops in patients with liver cirrhosis and passively requires ventilation support during the perioperative period of liver transplantation.[13] Liver transplantation is the ultimate treatment for HPS because arterial oxygenation owing to HPS normalizes following liver transplantation.[16] However, no patient with HPS was admitted to our ICU before liver transplantation.

In our study, three-quarters of critically ill patients with LF required CRRT, and the need for CRRT was higher in the V group than in the no-V group. Furthermore, CRRT was performed for both hepatic encephalopathy in fulminant hepatic failure and LF-associated acute renal injury. Mechanical ventilation was required for various reasons, including volume overload, respiratory failure, and hepatic encephalopathy. Thus, we infer that there may be considerable overlap and complementarity between the reasons for mechanical ventilation and CRRT.

In our study, the APACHE-II score was superior to the liver-specific scores of the Child–Pugh and MELD assessments for predicting the need for mechanical ventilation. Reasons for mechanical ventilation included not only factors that were directly associated with liver diseases, including hepatic encephalopathy, but also other factors, such as lung edema and sepsis. Therefore, the scores evaluating multiorgan failure could be superior to those assessing LF only. Some reports have evaluated the predictive power of various scoring models for patient outcomes. They mostly concluded that those general prognostic models, such as APACHE-II, APACHE-III, and SOFA, perform better in predicting the mortality of cirrhotic patients in ICU than liver-specific scores such as Child–Pugh and MELD scores.[28] O'Brien et al. reported that the APACHE-II score underpredicts mortality in liver cirrhosis patients.[8] Besides those obtained on the day of ICU admission, SOFA scores can help evaluate the diachronic transition of a patient's status by multiorgan failure. In this study, SOFA scores worsened at the time of intubation compared with that at ICU admission in 8 patients, excluding those intubated on the ICU admission day, suggesting that the SOFA score is useful for identifying the timing of intubation, whereas APACHE-II scores can predict whether patients with LF require intubation during their ICU stay.

This study had some limitations. First, this was a retrospective analysis undertaken at one center, and it evaluated a limited number of patients. Second, the patients were heterogeneous, including those having various types of LF. Critically ill patients with LF could often be excluded as targets for treatment because of severely poor general conditions. Therefore, intensivists usually experience a small

number of patients with severe LF. Reports establishing optimal management for such patients are limited. Since the included patients comprised both those with ALF and CLF, findings could be practically and clinically helpful. However, further investigation is needed to identify patients who can be adequately treated by invasive mechanical ventilation before liver transplantation.

In conclusion, critically ill patients with LF comprised a small proportion of patients at our general ICU and had multiorgan failure with poor outcomes. However, invasive mechanical ventilation did not have a negative effect on 90-day survival rates and performance rates of liver transplantation. Clinicians should not hesitate to provide mechanical ventilation-based life support for critically ill patients with LF who are on a waitlist for liver transplantation.

AUTHOR CONTRIBUTIONS

Atsuyoshi Mita: Conceptualization; formal analysis; investigation; visualization; writing—original draft. **Sari Shimizu**: Data curation; investigation; writing—review and editing. **Takashi Ichiyama**: Writing—review and editing. **Takateru Yamamoto**: Investigation. **Akinori Yamaguchi**: Data curation; investigation. **Kosuke Sonoda**: Writing—review and editing. **Kotaro Mori**: Writing—review and editing. **Tomokatsu Yamada**: Investigation. **Hiroyuki Nakamura**: Investigation; writing—review and editing. **Hiroshi Imamura**: Project administration; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shinshu University (3-1-1 Asahi, 390-8621, Matsumoto, Japan) on March 22, 2022 (registration number: 5449).

TRANSPARENCY STATEMENT

The lead author Atsuyoshi Mita affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Atsuyoshi Mita https://orcid.org/0000-0002-7078-7609

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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