Received: 16 May 2022 | Revised: 14 October 2022 | Accepted: 21 October 2022

DOI: 10.1111/hepr.13848

ORIGINAL ARTICLE

Hepatology Research JSH

Early-phase prothrombin time-international normalized ratio in acute liver injury indicates the timing of therapeutic intervention and predicts prognostic improvement

Kotaro Kumagai[1] | Seiichi Mawatari[1] | Akihiro Moriuchi[2] | Kohei Oda[1] | Yasuhiro Takikawa[3] | Naoya Kato[4] | Shigeto Oda[5] | Kazuaki Inoue[6] | Shuji Terai[7] | Takuya Genda[8] | Masahito Shimizu[9] | Isao Sakaida[10] | Satoshi Mochida[11] | Akio Ido[1]

[1]Digestive and Lifestyle Diseases, Department of Human and Environmental Sciences, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

[2]Department of Gastroenterology, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan

[3]Division of Hepatology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan

[4]Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan

[5]Department of Emergency Medicine, Chiba Kaihin Municipal Hospital, Chiba, Japan

[6]Department of Gastroenterology, International University of Health and Welfare Narita Hospital, Chiba, Japan

[7]Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan

[8]Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital, Shizuoka, Japan

[9]Department of Gastroenterology, Gifu University Graduate School of Medicine, Gifu, Japan

[10]Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine, Yamaguchi, Japan

[11]Department of Gastroenterology and Hepatology, Saitama Medical University, Saitama, Japan

Correspondence
Kotaro Kumagai, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan.
Email: kumakou@m2.kufm.kagoshima-u.ac.jp

Funding information
MHLW Research Program on Intractable Hepatobiliary Disease, Grant/Award Number: JPMH20FC1023; MSD K.K.; Toray Industries; EA Pharma Co., Ltd.

Abstract

Aim: We investigated whether an early-phase prothrombin time-international normalized ratio (PT-INR) is an interventional prognostic indicator for patients with acute liver injury, including acute liver failure.

Methods: This was a multicenter retrospective observational study. We included 595 patients with alanine aminotransferase levels ≥300 U/L due to acute liver injury who were admitted to Kagoshima University Hospital or other collaborative investigation organizations between January 1, 2010, and December 31, 2015. Patients with alanine aminotransferase levels ≥300 U/L and no previous liver disease were defined as having an acute liver injury. Acute liver failure was defined by

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; ALF, acute liver failure; ALI, acute liver injury; ALT, alanine aminotransferase; AUROC, area under these ROC curve; DILI, drug-induced liver injury; D/T, direct bilirubin/total bilirubin; EASL, European Association for the Study of the Liver; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; HEV, hepatitis E virus; HR, hazard ratio; INR, international normalized ratio; LT, liver transplantation; MELD, Model for End-stage Liver Disease; NPV, negative predictive value; PPV, positive predictive value; PT, prothrombin time; ROC, receiver operating characteristic; TFS, transplant-free survival.

PT-INR ≥1.5 with or without hepatic encephalopathy in acute liver injury patients. Data were obtained retrospectively from case reports and analyzed.

Results: The PT-INR on day 1 was the most accurate independent prognosis predictor in patients with acute liver injury and acute liver failure. On day 1, the transplant-free survival rates were significantly lower in patients with PT-INR ≥1.3. The transplant-free survival rates were also significantly higher in patients with acute liver injury and acute liver failure, in whom the PT-INR had recovered from ≥1.3 on day 1 to <1.3 by day 8.

Conclusion: Early-phase changes in the PT-INR can predict the prognosis of patients with acute liver injury and acute liver failure. Furthermore, PT-INR ≥1.3 could be an interventional marker, whereas PT-INR <1.3 after 1 week could reflect prognostic improvement.

KEYWORDS
acute liver failure, acute liver injury, international normalized ratio, prognosis, prothrombin, treatment

INTRODUCTION

Acute liver failure is a critical disease associated with high mortality rates.[1,2] [Correction added on 12 December 2022, after first online publication: The term 'chronic' has been changed to 'critical' in the preceding sentence.]. Effective medication strategies that do not include initial etiology-specific therapy are currently unavailable. When etiology-specific therapies are ineffective, LT remains the only alternative for increasing survival rates in affected patients.[1] Therefore, patients with ALF should be hospitalized and monitored frequently, preferably in the intensive care unit.[3] Once ALF progresses, the prognosis is poor due to massive hepatocyte death and coagulopathy; it is too late to treat patients in whom the PT-INR has reached a value of ≥1.5. Ideally, the treatment should be initiated in the pre-ALF stage. However, only a few therapeutic agents, such as immunosuppressants and antiviral agents, are available for treating patients at the initial stage. Furthermore, no markers are available for determining the appropriate timing of the initial or additional treatment. No guidelines have been established specifying the optimal timing of the treatment, even for AIH and HBV infection in patients at a pre-ALF stage; however, specific treatments for these have been mentioned in the guidelines by the AASLD.[3]

In our previous study, we reported that the recovery of the PT-INR <1.3 by the last assessment predicts survival in patients with severe ALI.[4] Therefore, we focused on PT-INR as a surrogate marker for the optimal timing of therapeutic intervention. Prothrombin time is a universal indicator of severity in patients with ALF.[5–7] It is a diagnostic criterion for ALF[3,8,9] and a prognostic factor worldwide.[10] Moreover, the PT-INR can be measured very easily. Thus, if used as a surrogate marker for prognosis in patients with ALI and ALF, the PT-INR could aid in deciding the appropriate treatment timeline. We also hypothesized that early recovery of the PT-INR could indicate an improvement in prognosis.

In the present multicenter study based in Japan, we aimed to determine whether early-phase PT-INR can predict the appropriate timing for treatment and the prognostic improvement in a large cohort of patients with ALI and ALF. Previous reports have shown a relationship between ALF and PT-INR.[6,7] However, to our best knowledge, no study to date has analyzed the role of early-phase PT-INR in a large population of patients with ALI and ALF of each etiology.

METHODS

Study design and setting

This multicenter, retrospective, observational study screened 618 patients with ALI (including ALF; ALT levels ≥300 U/L) admitted to the Kagoshima University Hospital or nine collaborative investigation organizations between January 1, 2010 and December 31, 2015. All patients had PT-INR measured at least once. We excluded 23 patients with malignant tumors or an unclassified etiology. Accordingly, 595 patients were included in the analyses. A PT-INR value of 1.3 was used as the cut-off value during the analysis based on our previous report.[4] In Study 1, we investigated the prognosis of these 595 patients (305 patients with a PT-INR <1.3 and 290 patients with a PT-INR ≥1.3 on day 1, i.e., the first day of early-phase PT-INR measurement during the observation period). In Study 2, of the 290 patients with a PT-INR ≥1.3 on day 1, 167 patients for whom the PT-INR was measured on day 8 were selected, and their prognoses were investigated (Figure 1). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Kagoshima University Hospital Clinical Research Ethics Committee and the research ethics committee of each participating facility (approval number: 170238).

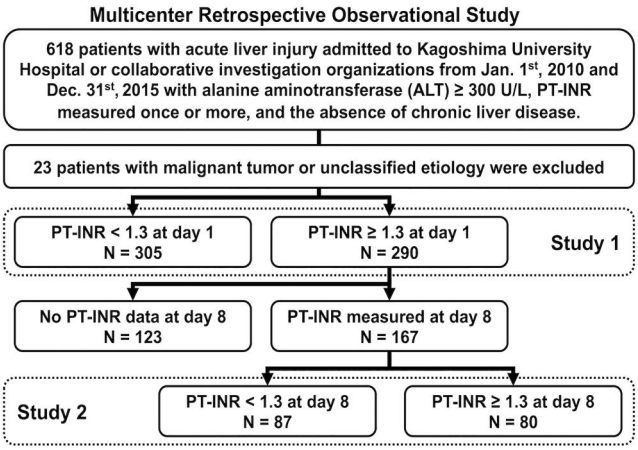

FIGURE 1 Study outline. This multicenter retrospective observational study screened a total of 618 patients. Day 1 was defined as the first day on which the prothrombin time-international normalized ratio (PT-INR) was measured during the observation period. In Studies 1 and 2, we assessed the transplant-free survival rates based on data for days 1 and 8 in patients with a PT-INR value ≥1.3 on day 1, respectively.

Definitions and criteria

A previous report showed that patients with ALT levels 10 times the upper reference limit typically have ALI.[11] In this study, patients with ALT ≥300 U/L and no previous liver disease were defined as having ALI. The etiologies were as follows: HAV, HBV, HCV, HEV, AIH, DILI, indeterminate, and ischemic liver injury. Hepatitis due to HAV and HEV was diagnosed by positive immunoglobulin M-HAV antibody and immunoglobulin A-HEV antibody, respectively. Acute HBV infection was defined as the elevation of transaminase level with positive immunoglobulin M-hepatitis B core antigen-antibody in patients not previously diagnosed as HBV carriers. Acute exacerbation of HBV infection was defined as increased transaminase level in patients previously diagnosed as HBV carriers and without evidence associated with other underlying chronic liver diseases. Acute HCV infection was diagnosed by positive HCV-RNA. Autoimmune hepatitis was diagnosed based on an international AIH score[12] and simplified AIH criteria.[13] Drug-induced liver injury was diagnosed using scores of the diagnostic scale of the DDW-Japan 2004 workshop[14,15] and the Roussel Uclaf Causality Assessment Method system (RUCAM score).[16] Acute liver failure was defined as a PT-INR ≥1.5 in a patient with no previous liver disease, with or without HE, per the diagnostic criteria for ALF and the classification of HE published by the Intractable Hepato-Biliary Diseases Study Group of Japan.[8,17,18] The observational period was the period between the day when patients got symptoms and the day when they recovered and were discharged. Outcomes included TFS, LT, or death. Transplant-free survival means that patients recovered and were discharged. As mentioned previously, day 1 was defined as the first day of PT-INR measurement; the PT-INR was measured as early as possible during the observational period. The MELD score was calculated using the following formula, based on the hematological examination results: MELD = 9.57 $\log_e$ (Cre [mg/dl]) + 3.78 $\log_e$ (total bilirubin [mg/dl]) + 11.20 $\log_e$ (PT-INR) + 6.43.

If the individual values were less than 1.0, they were set to 1.0; serum creatinine was adjusted to 4 mg/dl if the patients underwent dialysis for 2 weeks before assessment or in cases where the serum creatinine level was >4.0 mg/dl.[19]

Procedures

Using case reports collected from each collaborative organization, we extracted data on patients' sex, age, etiology, disease type, outcome, onset of symptoms and HE, date of LT, PT-INR, total bilirubin, direct bilirubin, D/T ratio, platelet count, ALT level, MELD score, date of plasma exchange, and date of hemodiafiltration during the observation period.

Data collection

All data were verified at least twice to determine whether the definitions and criteria were compatible.

Statistical analysis

Statistical analyses were undertaken using SPSS version 26 (IBM) and GraphPad Prism version 8.4.3 (GraphPad Software). The χ^2-test and Mann–Whitney *U*-test were used to evaluate the results' statistical significance. Univariate and multivariate competitive risk Cox regression models were used to identify the independent predictors of LT or death. Potential risk factors that were significant ($p < 0.05$) in the univariate analysis were included in the multivariate analysis to analyze the HR. Using ROC curves, we assessed whether these potential risk factors were useful as prognostic markers. Finally, the Kaplan–Meier and log–rank tests were used to analyze the cumulative TFS rates. Statistical significance was set at $p < 0.05$.

RESULTS

Study outline and patient characteristics

The median age of the 595 included patients was 54 years; female patients comprised 53% of the cohort. The median observation period was 30 days. The major cause of ALI was a viral infection, accounting for 35% of the cases. Acute liver injury, excluding ALF, was observed in 59% of the patients; ALF with and without HE was noted in 11% and 30% of the patients, respectively. Approximately 90% of the patients recovered, while 10% underwent LT or died. The PT-INR on day 1 was measured on a median of 7 days (range, −10 to 184 days) from the onset of symptoms (no data shown). Regarding

treatment, for 310 patients, steroid treatment was started on day 2 (median). For 82 patients, treatment with nucleoside/nucleotide analogs was started on day 1 (median); for 81 patients, treatment with plasma exchange and/or hemodiafiltration was started on day 1 (median; Table 1). In Study 1, 14 (5%) of the 305 patients with a PT-INR <1.3 on day 1 and 231 (80%) of the 290 patients with a PT-INR ≥1.3 on day 1 were ultimately diagnosed with ALF; 2 (1%) and 64 (22%) of these patients, respectively, developed HE. Moreover, 2 (1%) and 58 (20%) of these patients died or underwent LT (Table S2). In Study 2, of the 167 patients with a PT-INR ≥1.3 on day 1 and PT-INR value measured on day 8, 68 (78%) of the 87 patients with a PT-INR <1.3 on day 8 as well as 76 (95%) of the 80 patients with a PT-INR ≥1.3 on day 8 were ultimately diagnosed with ALF; 5 (6%) and 45 (56%) of these patients, respectively, developed HE. All five patients survived among those with a PT-INR ≥1.3 on day 1 and PT-INR <1.3 on day 8, whereas 43 (54%) patients who had a PT-INR value ≥1.3 on day 1 and on day 8 died or underwent LT (Table S3).

Prothrombin time-INR on day 1 was an independent prognostic factor in patients with ALI and ALF

To determine the timing of therapeutic intervention for patients with ALI and ALF (Study 1), we first identified the prognostic factors from day 1 data using univariate and multivariate competitive risk Cox regression models. Female sex, AIH, PT-INR, total bilirubin levels, platelet count, ALT levels, and MELD score were significant factors in the univariate analysis. When undertaking the multivariate analysis, including the MELD score, only the MELD score was an independent prognostic factor (HR 1.104; 95% CI, 1.058–1.151; $p < 0.001$). However, this analysis was confounding as the MELD score included PT-INR and total bilirubin. Moreover, we aimed to explore a novel and simple interventional indicator in patients with ALI in the pre-ALF stage. Therefore, we removed the MELD score from the multivariate analysis and chose PT-INR, total bilirubin, and platelet count, which have already been reported as prognostic factors in this study.[19] Furthermore, multivariate analysis identified PT-INR, total bilirubin, and platelet count as the independent prognostic predictors (Table 2). The PT-INR on day 1 (our focus) was an independent prognostic factor in patients with ALI and ALF.

Prothrombin time-INR on day 1 significantly predicted prognosis in patients with ALI and ALF

We used ROC curves, AUROCs, and *p* values to confirm the accuracy of age, PT-INR, total bilirubin levels, D/T ratio, platelet count, and ALT as prognostic predictors on day 1. This analysis identified age, PT-INR, total bilirubin, and platelet count as significant prognostic predictors. In addition, we used a DeLong test to assess whether there was a significant difference among the AUROCs of each

TABLE 1 Characteristics of patients with acute liver injury in Study 1 cohort

Total number of patients	*N* = 595
Duration of observation (days)	30 (1–455)
Age (years)	54 (9–88)
Sex	
Male	279 (47%)
Female	316 (53%)
Etiology	
Viral (HAV/HBV/HCV/HEV/Others)	211 (46/115/5/20/25) (35%)
AIH	124 (21%)
DILI	122 (21%)
Indeterminate	121 (20%)
Ischemic liver injury	17 (3%)
Final disease type	
ALI excluding ALF	350 (59%)
ALF without HE	179 (30%)
ALF with HE, acute type	30 (5%)
ALF with HE, subacute type	36 (6%)
Outcome	
Transplant-free survival	535 (90%)
Liver transplantation	13 (2.2%)
Death	47 (7.8%)
Laboratory data	
PT-INR (*n* = 595)	1.28 (0.8–18.9)
T-bilirubin (mg/dl) (*n* = 593)	5.1 (0.3–47.3)
D/T ratio (*n* = 533)	0.68 (0.10–0.95)
Platelet count ($\times 10^4$/ml) (*n* = 589)	17.3 (0.3–49.5)
ALT (U/L) (*n* = 595)	1343 (301–12, 119)
MELD score (*n* = 577)	16 (6–40)
Treatments and median when to start treatments	
Steroids (*n* = 310)	2 (−100–86)[a]
Nucleoside/nucleotide analogs (*n* = 82)	1 (−81–34)[a]
Plasma exchange and/or hemodiafiltration (*n* = 81)	1 (−6–77)[a]

Note: Etiology and disease type were defined per the diagnostic criteria in Japan. Outcomes and laboratory data are shown. Laboratory data are presented as medians and ranges.

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALI, acute liver injury; ALT, alanine aminotransferase; D/T, direct bilirubin/total bilirubin; DILI, drug-induced liver injury; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; HEV, hepatitis E virus; PT-INR, prothrombin time-international normalized ratio.

[a]The unit was "day" when to start treatments.

TABLE 2 Identification of independent prognostic factors on day 1 in patients with acute liver injury and acute liver failure

	Univariate analysis		Multivariate analysis	
Factor	**Hazard ratio (95% confidence interval)**	***p* value**	**Hazard ratio (95% confidence interval)**	***p* value**
Age, years	1.016 (1.000–1.033)	0.054	-	-
Sex				
Male	1.000			
Female	0.550 (0.330–0.919)	0.022*	-	-
Etiology				
Viral infection	1.000			
AIH	0.242 (0.098–0.597)	0.002**	-	-
DILI	0.733 (0.356–1.507)	0.398	-	-
Indeterminate	1.208 (0.644–2.264)	0.556	-	-
Ischemic liver injury	2.418 (0.723–8.083)	0.152	-	-
Laboratory data				
PT-INR	1.264 (1.207–1.324)	<0.0001****	1.330 (1.240–1.426)	<0.0001****
T-bilirubin (mg/dl)	1.054 (1.028–1.081)	<0.0001****	1.082 (1.050–1.116)	<0.0001****
D/T ratio	3.098 (0.523–18.344)	0.213	-	-
Platelet count ($\times 10^4$/ml)	0.927 (0.890–0.964)	<0.0001****	0.907 (0.868–0.948)	<0.0001****
ALT (U/L)	1.000 (1.000–1.000)	0.002**	-	-
MELD score	1.175 (1.142–1.212)	<0.0001****	-	-

Note: All laboratory data and Model for End-stage Liver Disease (MELD) scores were measured on day 1.

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; DILI, drug-induced liver injury; D/T, direct bilirubin/total bilirubin; PT-INR, prothrombintime-international normalized ratio.

*$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

parameter. Among these, the PT-INR significantly indicated the highest predictive accuracy. Conversely, the AUROC of the MELD score on day 1 was 0.8961, which was not significantly different from that of PT-INR on day 1 (Figure 2, Table S3). When the cut-off value was 1.3 of PT-INR on day 1, the distinction of prognosis for sensitivity, specificity, PPV, and NPV was 0.967, 0.566, 0.200, and 0.993, respectively (Table S4).

Transplant-free survival rate was significantly lower among patients with a PT-INR ≥1.3 than among those with a PT-INR <1.3 on day 1

Our previous analysis revealed that PT-INR <1.3 predicted survival in patients with severe ALI. In this study, we used the Kaplan–Meier and log–rank tests to investigate whether PT-INR ≥1.3 on day 1 could predict the prognosis in this population. The overall TFS rate was significantly lower in patients with a PT-INR ≥1.3 (median, 82 days) than in those with a PT-INR <1.3 (median, not reached) (Figure 3a), even when analyzed based on etiology (Figure 3b). Fifty-eight patients with PT-INR ≥1.3 on day 1 underwent LT or died (Table S1). Thirteen of those patients underwent LT; one of these 13 patients died after the transplantation. Of those, seven patients died due to nonliver-related causes; the remaining 38 died due to liver-related causes. Moreover, our study found that 25 (71%) of the 35 HBV-naïve patients with a PT-INR ≥1.5 on day 1 were treated with nucleoside/nucleotide analogs within 1 week from day 1, and 17 (81%) of the 21 patients with AIH and a PT-INR ≥1.5 were treated with steroids within 1 week from day 1. Seven (28%) of the 25 HBV-naïve patients with a PT-INR ≥1.5 on day 1 and 5 (29%) of the 17 patients with AIH and a PT-INR ≥1.5 died. In contrast, those with a PT-INR ≥1.3 to <1.5 on day 1 survived. These results were the same for patients with DILI or indeterminate etiology treated with steroids (Figure S1).

Prothrombin time-INR on day 8 was an independent prognostic factor in patients with ALI and ALF

To identify the markers of prognostic improvement in patients with ALI and ALF (Study 2), we analyzed the prognostic factors on day 8 in patients with a PT-INR ≥1.3 on day 1 using univariate and multivariate competitive risk Cox regression models. The PT-INR, total bilirubin levels, D/T ratio, platelet count, and MELD score were identified as significant factors in the univariate analysis. Consistent with Study 1, the MELD score was an independent prognostic factor

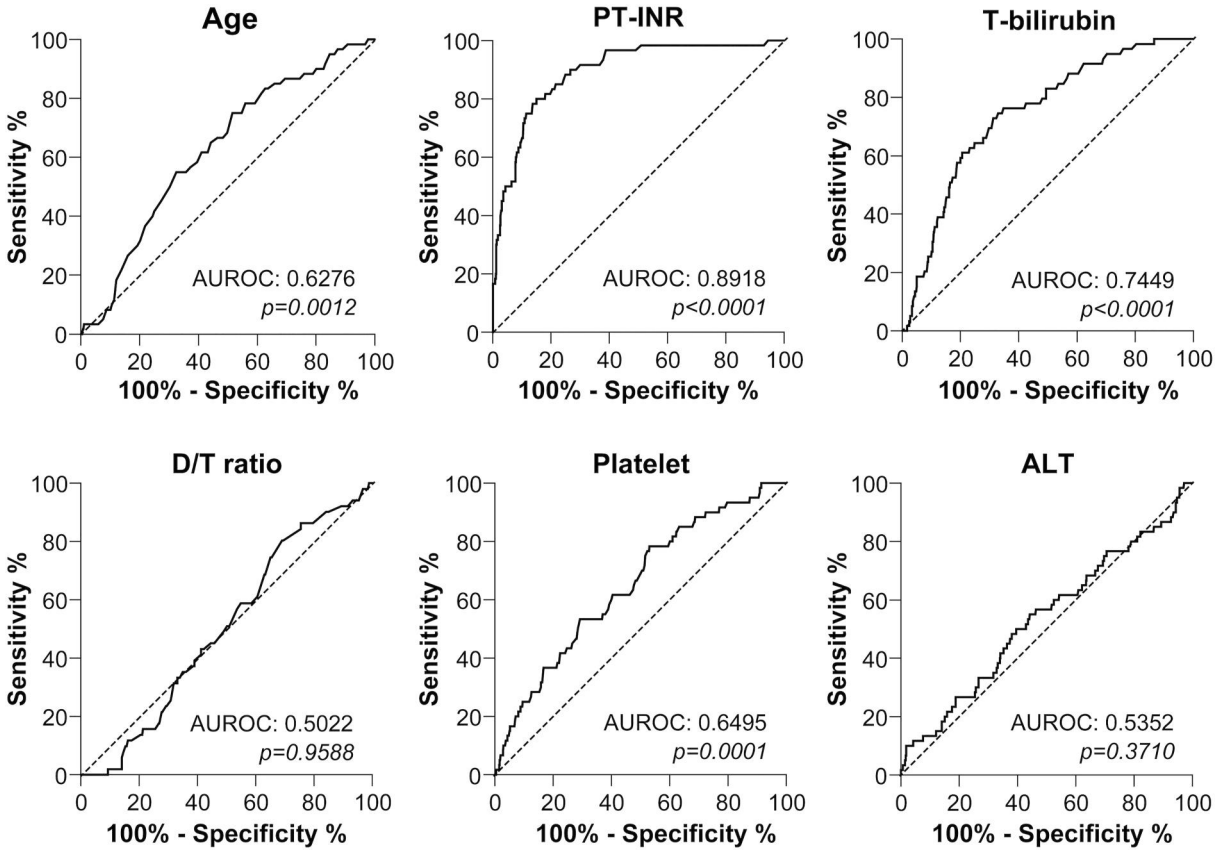

FIGURE 2 Prediction of prognosis in patients with acute liver injury analyzed by receiver operating characteristic (ROC) curves using age, prothrombin time-international normalized ratio (PT-INR), total bilirubin levels, direct bilirubin/total bilirubin (D/T) ratio, platelet count, and alanine aminotransferase (ALT) on day 1. The ROC curves for day 1 data were used to verify this. Areas under the ROC curves (AUROCs) and *p* values are shown in individual graphs.

when performing the multivariate analysis, including the MELD score (HR 1.099; 95% CI, 1.031–1.180; $p = 0.0059$). Based on our aim and previous report, as described previously, we removed the MELD score from multivariate analysis and chose the PT-INR, total bilirubin levels, D/T ratio, and platelet count, which have already been reported as prognostic factors in this study.[19] These factors were also revealed to be the independent prognostic predictors in the multivariate analysis (Table 3).

Prothrombin time-INR on day 8 significantly predicted prognosis in patients with ALI and ALF

We used the ROC curves, AUROCs, and *p* values to verify the accuracy of age, PT-INR, total bilirubin levels, D/T ratio, platelet count, and ALT as prognostic predictors on day 8. This analysis identified the aforementioned as significant prognostic factors. Among these, we used the DeLong test, similar to that in Study 1. As a result, PT-INR showed the highest predictive accuracy for the prognosis. Moreover, compared to the AUROC of PT-INR on day 1 using the DeLong test, that of PT-INR on day 8 showed significantly higher predictive accuracy. The AUROC of MELD score on day 8 was 0.946, which was not significantly different from the AUROC of PT-INR on day 8 (Figure 4, Table S1). When the cut-off value was 1.3 of PT-INR on day 8, the distinction of prognosis for sensitivity, specificity, PPV, and NPV was 1.000, 0.702, 0.538, and 1.000, respectively (Table S4).

Transplant-free survival rates were significantly higher in patients with recovery from PT-INR ≥1.3 on day 1 to <1.3 on day 8 than in those without such recovery

As in Study 1, we validated our findings using the Kaplan–Meier and log–rank tests to determine whether a PT-INR ≥1.3 on day 8 in patients with a similar value on day 1 could predict the prognosis. The overall TFS rate was significantly higher in patients with a PT-INR <1.3 than in those with a PT-INR ≥1.3. Moreover, all patients whose PT-INRs had recovered from ≥1.3 to <1.3 survived. The median TFS time was 55 days in patients with a PT-INR ≥1.3; however, in patients with a PT-INR <1.3, the median TFS time was not reached (Figure 5a). In addition, the TFS rates significantly differed between patients with an HBV-naïve etiology and those with an undetermined etiology as well as between patients with a PT-INR ≥1.3 and those with a PT-INR <1.3. Due to the small number of patients with AIH,

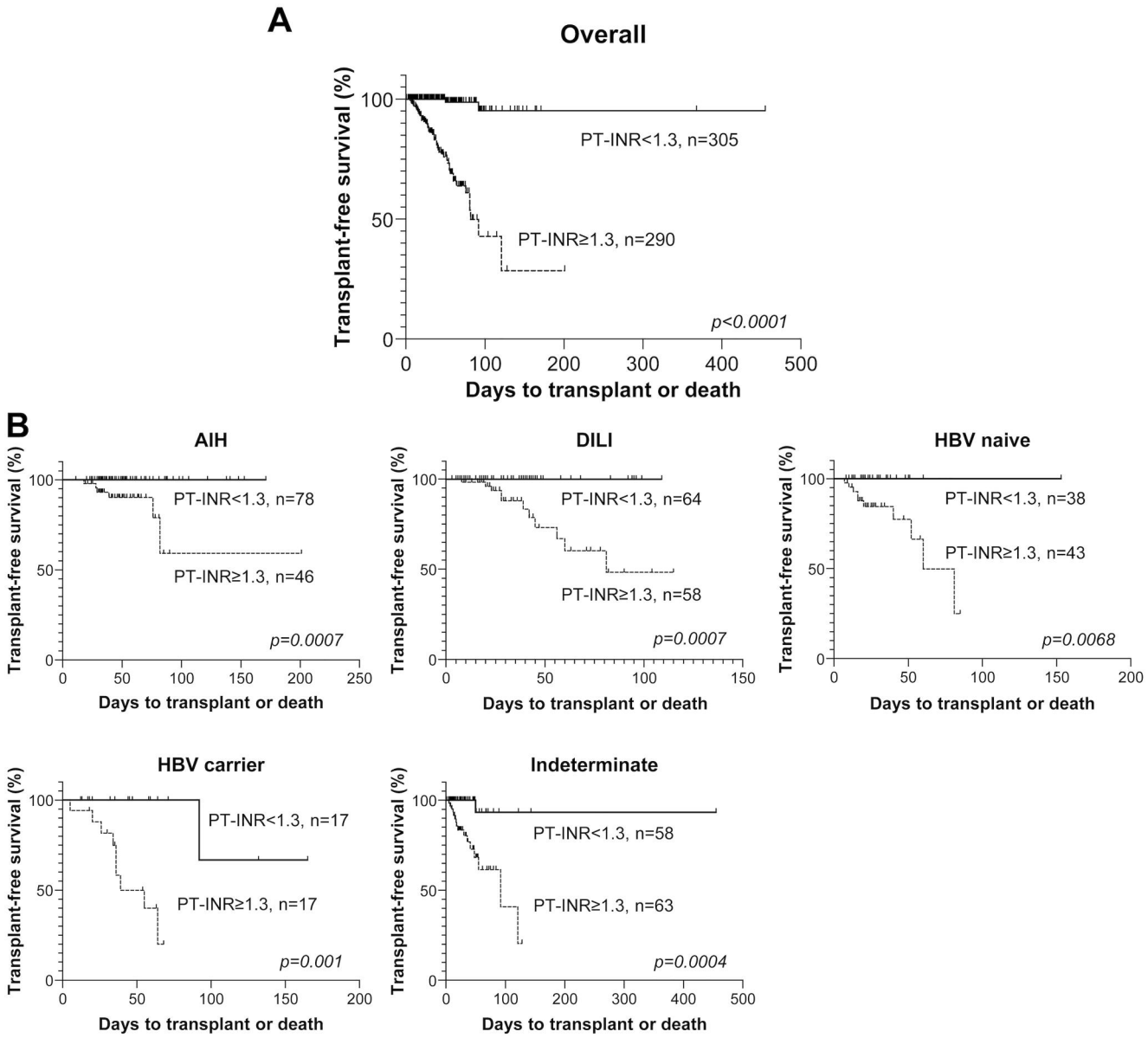

FIGURE 3 Cumulative rate of transplant-free survival in patients with acute liver injury (ALI), including acute liver failure (ALF), on day 1. (a) The Kaplan–Meier method and log–rank test were used to compare survival rates between patients with a prothrombin time-international normalized ratio (PT-INR) value <1.3 ($n = 305$) and those with a PT-INR value ≥1.3 ($n = 290$). Only two patients with a PT-INR value <1.3 died (causes: ALF, 1; pneumocystis pneumonia, 1). (b) Transplant-free survival rates were compared based on etiology (autoimmune hepatitis [AIH], drug-induced liver injury [DILI], hepatitis B virus [HBV]-naïve, HBV carrier, and indeterminate). *p* values are presented in individual graphs.

DILI, and HBV carrier status, we only observed trends toward increased TFS rates in patients with a PT-INR <1.3 compared to those with a PT-INR ≥1.3 (Figure 5b).

DISCUSSION

In the present study, we investigated whether PT-INR is an interventional indicator and reflects the prognosis of patients with ALI and ALF. Our findings indicate that early-phase PT-INR was a significant predictor of prognosis in this population. We observed significant differences in the prognosis between patients with a PT-INR ≥1.3 and those with a PT-INR <1.3. Moreover, patients in whom the PT-INR recovered from ≥1.3 on day 1 to <1.3 by day 8 had a higher TFS rate than those without such a recovery. The dynamics of early-phase PT-INR can predict prognosis and prognostic improvement.

First, we clarified that PT-INR on day 1 was an independent prognostic factor and predicted prognosis in patients with ALI and ALF. Considering the fact that the total number of events was 60 in this cohort (including LT and death), we chose the PT-INR, total bilirubin, and platelet count associated with prognosis based on the previous report.[19] Recent studies have used the MELD score as an early predictor of fulminant hepatic failure or ALF.[20,21] In the univariate analysis of this study, the MELD score was a prognostic factor.

TABLE 3 Identification of independent prognostic factors on day 8 in patients with acute liver injury and acute liver failure

	Univariate analysis		Multivariate analysis	
Factor	**Hazard ratio (95% confidence interval)**	***p* value**	**Hazard ratio (95% confidence interval)**	***p* value**
Age, years	1.015 (0.995–1.036)	0.134	-	-
Sex				
Male	1.000			
Female	0.663 (0.358–1.229)	0.192	-	-
Etiology				
Viral infection	1.000			
AIH	0.504 (0.168–1.515)	0.223	-	-
DILI	1.053 (0.474–2.340)	0.899	-	-
Indeterminate	0.731 (0.316–1.691)	0.463	-	-
Ischemic liver injury	1.270 (0.358–4.449)	0.711	-	-
Laboratory data				
PT-INR	1.785 (1.493–2.133)	<0.0001****	1.459 (1.072–1.973)	0.016*
T-bilirubin (mg/dl)	1.071 (1.033–1.110)	<0.0001****	1.053 (1.004–1.105)	0.035*
D/T ratio	0.025 (0.006–0.107)	<0.0001****	0.140 (0.024–0.802)	0.027*
Platelet count ($\times 10^4$/ml)	0.859 (0.810–0.910)	<0.0001****	0.880 (0.828–0.935)	<0.0001****
ALT (U/L)	1.000 (0.999–1.000)	0.180	-	-
MELD score	1.182 (1.130–1.246)	<0.0001****	-	-

Note: All laboratory data and Model for End-stage Liver Disease (MELD) scores were measured on day 8.

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; DILI, drug-induced liver injury; D/T, direct bilirubin/total bilirubin; PT-INR, prothrombintime-international normalized ratio.

*$p < 0.05$, ****$p < 0.0001$.

Moreover, only the MELD score was an independent prognostic factor when performing the multivariate analysis. However, this analysis was confounding among the MELD score, PT-INR, and total bilirubin levels. Moreover, there was no significant difference between the AUROC of PT-INR and the MELD score on days 1 and 8. Therefore, we did not include the MELD score in the multivariate analysis. The PT-INR value is not necessary to calculate, and it is simpler to indicate the timing of therapeutic intervention and the prediction of prognostic improvement compared with the MELD score.

There is limited knowledge regarding the sensitivity and specificity of the prognostic score in patients with ALI and ALF. Kakisaka et al. showed that the AUROC value to assess the prediction for disease progression was 0.617 for the MELD score and 0.745 for the PT-INR in patients with ALI who had PT-INR values of 1.2–1.5. The distinction of disease progression for sensitivity, specificity, PPV, and NPV was 0.630, 0.610, 0.347, and 0.833, respectively, for the MELD score and 0.740, 0.659, 0.417, and 0.901, respectively, for the PT-INR.[22] Although they evaluated the prediction of disease progression, the MELD score and PT-INR could predict disease progression, leading to poor prognosis in patients with ALI with PT-INR values of 1.2–1.5. Moreover, Bechmann et al. reported that the AUROC value to assess the prediction for prognosis was 0.808 for the MELD score and 0.801 for the PT-INR in patients with ALF. The distinction of prognosis for sensitivity and specificity were 0.750 and 0.711, respectively, for the MELD score, and 0.833 and 0.736, respectively, for PT-INR.[23] This report was analyzed only with patients with ALF; there was no difference in the AUROCs between the MELD score and the PT-INR. However, the sensitivity and specificity for the PT-INR value were higher than those for the MELD score. In our study, the AUROCs of PT-INR on days 1 and 8 were 0.892 and 0.946, respectively. These data were higher than those in previous reports; one of the reasons was that our study included patients with ALI and ALF. Conversely, when the cut-off was PT-INR $\geq$1.3 on days 1 and 8, the sensitivity and NPVs were higher, and the specificity and PPVs were lower than those in previous reports. We believed this was suitable for an interventional marker to start treatments and a marker of prognostic improvement in patients with ALI and ALF. In addition, it has been reported that liver atrophy was a prognostic factor for ALF in adults.[24] The finding of liver atrophy is useful to predict the prognosis and indicate LT. However, liver atrophy reflects irreversible hepatocyte damage. Therefore, this is unsuitable for predicting the prognosis and initiating treatments for ALI.

A previous report showed that 59.4%–77.6% of patients with ALF were treated with steroids; 76.7%–77.9% of those underwent

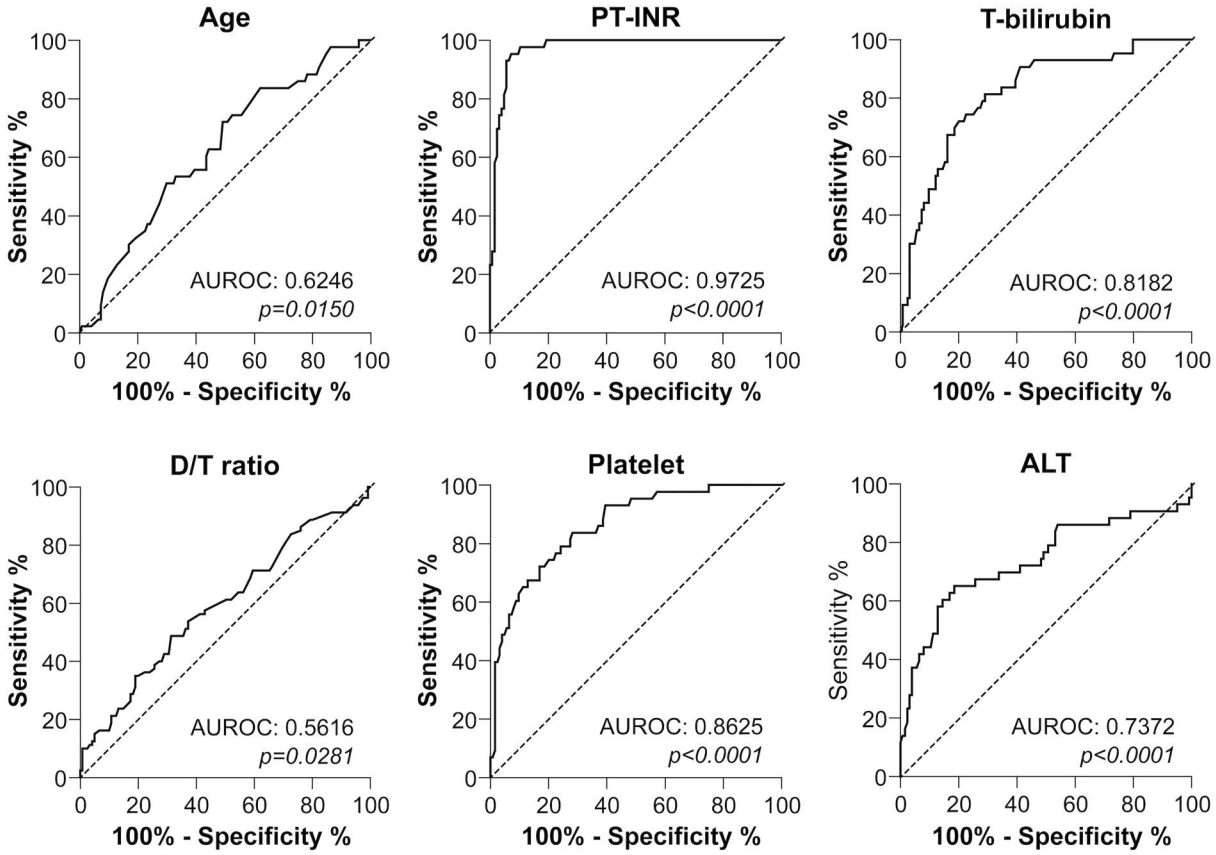

FIGURE 4 Prediction of prognosis analyzed by receiver operating characteristic (ROC) curve using age, prothrombin time-international normalized ratio (PT-INR), total bilirubin levels, direct bilirubin/total bilirubin (D/T) ratio, platelet count, and alanine aminotransferase (ALT) on day 8. ROC curves for day 8 data were used to verify this. The areas under the ROC curves (AUROCs) and *p* values are presented in individual graphs.

plasma exchange, while 73.7%–75.4% underwent hemodiafiltration in Japan.[1] In this study, we collected data on steroids, plasma exchange, hemodiafiltration, and nucleoside/nucleotide analogs for HBV infection. There were no same treatment criteria and timing at each facility in this study, as there is no gold standard strategy to treat ALI/ALF at present. Moreover, there might have been some bias due to the timing of treatments. However, even though the timing of starting steroids and nucleoside/nucleotide analogs within 1 week from day 1 was adjusted, patients with PT-INR ≥1.5 on day 1 had a poor prognosis compared with those with PT-INR values ranging from ≥1.3 to <1.5 on day 1. This finding shows that patients with PT-INR ≥1.5 may have a poor prognosis, even on etiology-specific medications, regardless of whether they initiated treatments during the early phase. In addition, Fujiwara et al. reported that a critical point for evaluating the efficacy of steroid treatment and switching to LT in patients with ALF with AIH was at the most 2 weeks after diagnosis of ALF and introduction of steroid treatment, because of complications related to infection.[25] This might also affect prognosis in patients with PT-INR ≥1.5. In contrast, patients with ALI may survive when starting treatments before reaching a PT-INR value of ≥1.5. Patients with PT-INR ≥1.5 and HE undergo artificial liver support, such as plasma exchange and hemodiafiltration, to recover consciousness from HE, which does not induce liver regeneration and is not reported to contribute to survival without LT.[26] Therefore, we believe that the most important thing was to initiate treatments during the early phase of liver injury, not the time course. If PT-INR is measured for patients with ALI in the pre-ALF stage, starting treatments during the early phase might help to avoid LT. This is especially important in Japan, given the low number of brain-dead donors and long waiting time of recipients.[27,28]

Our study had several strengths. It is the largest case series on the use of early-phase PT-INR for assessing the prognosis of patients with ALI and ALF. According to the EASL and AASLD guidelines, the definition of ALF requires the presence of HE. In patients with ALF without ALI, it has been recently reported that combining biomarkers with current models, such as the MELD score, has prognostic value.[29] However, we classified patients as having ALF, including patients without HE, based on the definition of the Intractable Hepato-Biliary Diseases Study Group of Japan. Therefore, the results of our study were different from those obtained in works using definitions of ALF according to the EASL and AASLD guidelines. Conversely, clinical practice guidelines from the EASL stated that biomarkers can help predict the progression from ALI to ALF in future studies.[9] Early-phase PT-INR could serve as one such biomarker for the progression of ALI to ALF.

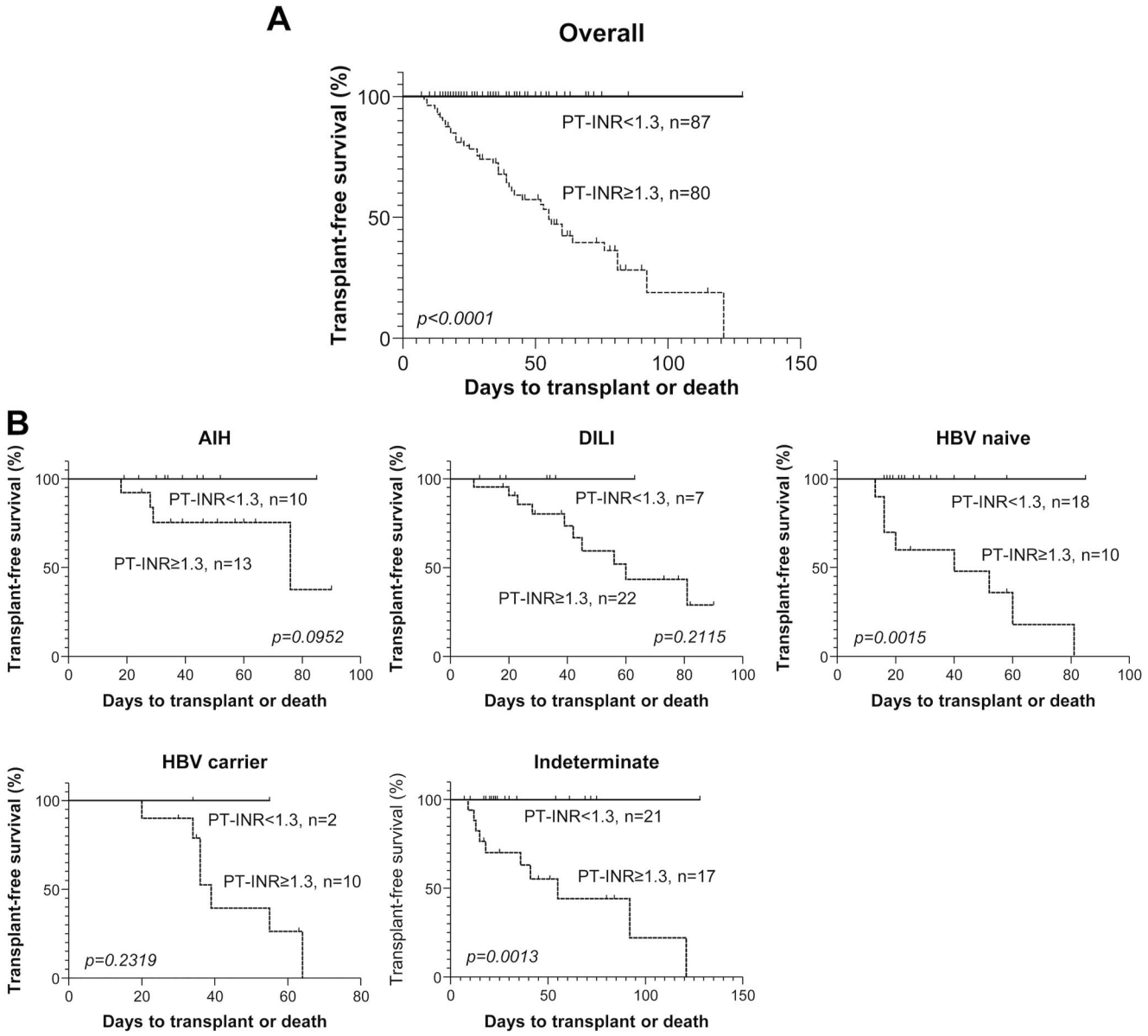

FIGURE 5 Cumulative rate of transplant-free survival in patients with acute liver injury, including acute liver failure, on day 8. (a) Kaplan–Meier method and log–rank test were used to compare survival rates between patients with a prothrombin time-international normalized ratio (PT-INR) value <1.3 ($n = 87$) and those with a PT-INR value ≥1.3 ($n = 80$). (b) Transplant-free survival rates were compared based on etiology (autoimmune hepatitis [AIH], drug-induced liver injury [DILI], hepatitis B virus [HBV]-naïve, HBV carrier, and indeterminate). *p*-values are presented in individual graphs.

The present study had some limitations, including its retrospective design. Although additional prospective studies may be required, we analyzed data from a large cohort of patients across multiple centers. Thus, our data could be close to the data observed in real-world clinical settings. Furthermore, the study may have been affected by bias due to the definition of "day 1." Day 1 was defined as the day of the first PT-INR measurement during the observation period; this meant that the PT-INR might have been measured in the early phase for some patients and the middle phase for others. However, it is difficult to adjust the timing of the first measurement of PT-INR. In clinical practice, many patients with ALI are asymptomatic, and the PT-INR is typically measured once patients begin experiencing symptoms or visit the clinic or hospital. Nonetheless, our findings suggest that measuring changes in the PT-INR during the early phase after the appearance of symptoms or after a clinical or hospital visit can aid in predicting prognosis.

In conclusion, a PT-INR value ≥1.3 during the early phase could be an indicator to initiate the therapeutic intervention, while a PT-INR value <1.3 after 1 week may reflect prognostic improvement in patients with ALI, including ALF. Moreover, these findings are not affected by etiologies. In the future, a PT-INR value ≥1.3 could be useful as an early interventional marker and an early prognostic marker in clinical practice and studies designed to assess current and new therapeutic strategies for patients with ALI and ALF.

ACKNOWLEDGMENTS

This work was supported by the MHLW Research Program on Intractable Hepatobiliary Disease, Grant Number JPMH20FC1023.

CONFLICT OF INTEREST

Takuya Genda received honoraria from AbbVie GK, Gilead Sciences Inc., and MSD K.K., as well as research funding from AbbVie GK, Otsuka Pharmaceutical, Mitsubishi Tanabe Pharma, JIMRO, and Takeda Pharmaceutical. Satoshi Mochida received honoraria from AbbVie GK, Gilead Sciences Inc., MSD K.K., Otsuka Pharmaceutical Co. Ltd., Sumitomo Pharma Co. Ltd., Eisai Co. Ltd., Toray Industries Inc., and ASKA Pharmaceutical Co. Ltd. as well as research funding from Gilead Sciences Inc., EA Pharma Co. Ltd., AbbVie GK, Sumitomo Pharma Co. Ltd., Toray Industries Inc., Eisai Co. Ltd., ASKA Pharmaceutical Co. Ltd., EPS International Holdings Co. Ltd., MSD K.K., and Intellim Corporation. The funders had no role in the study design, data collection and analysis, publication decision, or manuscript preparation. The other authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICS STATEMENTS

Approval of the research protocol: The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Kagoshima University Hospital Clinical Research Ethics Committee and the research ethics committee of each participating facility (approval number: 170238).

Informed consent: Informed consent was obtained in the form of opt-out on the website.

Registry and registration no. of the study/trial: N/A

Animal studies: N/A

Research involving recombinant DNA: N/A

ORCID

Kotaro Kumagai https://orcid.org/0000-0001-9532-7580
Seiichi Mawatari https://orcid.org/0000-0002-3847-1065
Yasuhiro Takikawa https://orcid.org/0000-0002-1729-1540
Takuya Genda https://orcid.org/0000-0003-0006-8948

REFERENCES

1. Nakao M, Nakayama N, Uchida Y, Tomiya T, Ido A, Sakaida I, et al. Nationwide survey for acute liver failure and late-onset hepatic failure in Japan. J Gastroenterol. 2018;53(6):752–69. https://doi.org/10.1007/s00535-017-1394-2
2. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369(26):2525–34. https://doi.org/10.1056/NEJMra1208937
3. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012;55(3):965–7. https://doi.org/10.1002/hep.25551
4. Mawatari S, Moriuchi A, Ohba F, Kawano T, Oda K, Takikawa Y, et al. The recovery of the PT-INR to less than 1.3 predicts survival in patients with severe acute liver injury. J. Gastroenterol. 2018;53(7):861–72. https://doi.org/10.1007/s00535-017-1421-3
5. O'Grady JG, Gimson AE, O'Brien CJ, Pucknell A, Hughes RD, Williams R. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. Gastroenterology. 1988;94(5):1186–92. https://doi.org/10.1016/0016-5085(88)90011-x
6. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97(2):439–45. https://doi.org/10.1016/0016-5085(89)90081-4
7. Robert A, Chazouillères O. Prothrombin time in liver failure: time, ratio, activity percentage, or international normalized ratio. Hepatology. 1996;24(6):1392–4. https://doi.org/10.1053/jhep.1996.v24.pm0008938167
8. Sugawara K, Nakayama N, Mochida S. Acute liver failure in Japan: definition, classification, and prediction of the outcome. J Gastroenterol. 2012;47(8):849–61. https://doi.org/10.1007/s00535-012-0624-x
9. Wendon J, Cordoba J, Dhawan A, Larsen FS, Manns M, Samuel D, et al. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047–81. https://doi.org/10.1016/j.jhep.2016.12.003
10. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31(4):864–71. https://doi.org/10.1053/he.2000.5852
11. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. CMAJ. 2005;172(3):367–79. https://doi.org/10.1503/cmaj.1040752
12. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31(5):929–38. https://doi.org/10.1016/s0168-8278(99)80297-9
13. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, et al. International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48(1):169–76. https://doi.org/10.1002/hep.22322
14. Takikawa H, Onji M, Takamori Y, Murata Y, Taniguchi H, Ito T, et al. Proposal of diagnostic criteria for drug-induced liver injury revised by the DDW-J 2004 Workshop. Kanzo. 2005;85–90(2):486. (In Japanese). https://doi.org/10.2957/kanzo.46.85
15. Takikawa H, Onji M. A proposal of the diagnostic scale of drug-induced liver injury. Hepatol Res. 2005;32(4):250–1. https://doi.org/10.1016/j.hepres.2005.05.007
16. Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci. 2015;17(1):14. https://doi.org/10.3390/ijms17010014
17. Mochida S, Takikawa Y, Nakayama N, Oketani M, Naiki T, Yamagishi Y, et al. Diagnostic criteria of acute liver failure: a report by the Intractable Hepato-Biliary Diseases Study Group of Japan. Hepatol Res. 2011;41(9):805–12. https://doi.org/10.1111/j.1872-034X.2011.00860.x
18. Fujiwara K, Yasui S, Yonemitsu Y, Mikata R, Arai M, Kanda T, et al. Efficacy of high-dose corticosteroid in the early stage of viral acute liver failure. Hepatol Res. 2014;44(5):491–501. https://doi.org/10.1111/hepr.12148
19. Naiki T, Nakayama N, Mochida S, Oketani M, Takikawa H, Suzuki K, et al. Novel scoring system as a useful model to predict the outcome of patients with acute liver failure: application to indication criteria for liver transplantation. Hepatol Res. 2012;42(1):68–75. https://doi.org/10.1111/j.1872-034X.2011.00902.x
20. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70. https://doi.org/10.1053/jhep.2001.22172

21. Dhiman RK, Jain S, Maheshwari U, Bhalla A, Sharma N, Ahluwalia J, et al. Early indicators of prognosis in fulminant hepatic failure: an assessment of the model for end-stage liver disease (MELD) and King's College Hospital criteria. Liver Transpl. 2007;13(6):814–21. https://doi.org/10.1002/lt.21050
22. Kakisaka K, Suzuki Y, Kataoka K, Okada Y, Miyamoto Y, Kuroda H, et al. Predictive formula of coma onset and prothrombin time to distinguish patients who recover from acute liver injury. J Gastroenterol Hepatol. 2018;33(1):277–82. https://doi.org/10.1111/jgh.13819
23. Bechmann LP, Jochum C, Kocabayoglu P, Sowa JP, Kassalik M, Gieseler RK, et al. Cytokeratin 18-based modification of the MELD score improves prediction of spontaneous survival after acute liver injury. J Hepatol. 2010;53(4):639–47. https://doi.org/10.1016/j.jhep.2010.04.029
24. Yamagishi Y, Saito H, Ebinuma H, Kikuchi M, Ojiro K, Kanamori H, et al. A new prognostic formula for adult acute liver failure using computer tomography-derived hepatic volumetric analysis. J Gastroenterol. 2009;44(6):615–23. https://doi.org/10.1007/s00535-009-0045-7
25. Fujiwara K, Nakayama N, Kato N, Yokosuka O, Tsubouchi H, Takikawa H, et al. Infectious complications and timing for liver transplantation in autoimmune acute liver failure in Japan: a subanalysis based on nationwide surveys between 2010 and 2015. J Gastroenterol. 2020;55(9):888–98. https://doi.org/10.1007/s00535-020-01699-3
26. Fujiwara K, Abe R, Yasui S, Yokosuka O, Kato N, Oda S. High recovery rate of consciousness by high-volume filtrate hemodiafiltration for fulminant hepatitis. Hepatol Res. 2019;49(2):224–31. https://doi.org/10.1111/hepr.13255
27. Yoshimura N, Okajima H, Ushigome H, Sakamoto S, Fujiki M, Okamoto M. Current status of organ transplantation in Japan and worldwide. Surg Today. 2010;40(6):514–25. https://doi.org/10.1007/s00595-009-4214-3
28. Genda T, Ichida T, Sakisaka S, Tanaka E, Mochida S, Ueno Y, et al. Outcome of patients with acute liver failure awaiting liver transplantation in Japan. Hepatol Res. 2020;50(10):1186–95. https://doi.org/10.1111/hepr.13549
29. De Clercq P, Geerts A, Van Vlierberghe H, Verhelst X. The utility of biomarkers in prognosis assessment of patients with acute liver failure. Hepatol Res. 2021;51:750–7. https://doi.org/10.1111/hepr.13668

SUPPORTING INFORMATION

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

How to cite this article: Kumagai K, Mawatari S, Moriuchi A, Oda K, Takikawa Y, Kato N, et al. Early-phase prothrombin time-international normalized ratio in acute liver injury indicates the timing of therapeutic intervention and predicts prognostic improvement. Hepatol Res. 2022;1–12. https://doi.org/10.1111/hepr.13848