A predictive formula of coma onset and prothrombin time to distinguish patients who recover from acute liver injury

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Abstract

Background & Aim: Acute liver failure (ALF) is defined as acute liver injury (ALI) associated with coagulopathy. A follow-up strategy for ALI and characterization of ALI patients with a risk of progressing to ALF have never been established. To establish predictive markers for progression from ALI to ALF, we compared the clinical characteristics and laboratory data on the day of registration to data from a regional referral system of patients with ALI.

Methods: This prospective, observational study enrolled 365 consecutive patients with ALI/ALF between 2007 and 2016. We evaluated 109 ALI patients, 27 of whom satisfied the ALF criteria during observation and another 82 patients who recovered without progression to ALF.

Results: Four patients died; all were in the ALF group. The variables of age, incidence of autoimmune hepatitis, model of end-stage liver disease (MELD) score, values for total bilirubin and prothrombin time-international ratio (PT-INR), and Japan Hepatic Encephalopathy Prediction Model (JHEPM) probability at registration were significantly higher in ALF patients than in ALI patients. In multivariate analysis, PT and JHEPM were identified as risk factors for progression to ALF. The cut-off values of 13, 4.9%, 65%, and 1.32 for the MELD score, JHEPM probability, PT, and PT-INR values, respectively, had high negative predictive values. Furthermore, among patients whose JHEPM was underestimated, none died due to ALF.

Conclusion: JHEPM probability is a predictive parameter that can be used to decide a follow-up treatment strategy for ALI patients.

Abbreviations: Acute liver failure (ALF), acute liver injury (ALI), alanine aminotransferase (ALT), aspartate transaminase (AST), area under the receiver operating characteristic curve (AUROC), autoimmune hepatitis (AIH), drug-induced liver injury (DILI), Japan Hepatic Encephalopathy Prediction Model (JHEPM), creatinine (Cre), models of end-stage liver disease (MELD), negative predictive value (NPV), positive predictive value (PPV). prothrombin time activity (PT), prothrombin time-international normalized ratio (PT-INR), receiver–operator characteristic curve (ROC), total bilirubin (TBil).

Introduction

Acute liver failure (ALF) is manifested by the presence of coagulopathy (prothrombin time [PT]-international normalized ratio [PT-INR] > 1.5 or PT < 40%), occurring within 8 weeks of onset of symptoms in patients without underlying liver disease.[1] Progression to liver failure leads to detoxification, which results in hepatic coma.[2] Although ALF patients with coma are treated with intensive care such as artificial liver support, their mortality remains high without liver transplantation.[3, 4] Recently, it has been reported that early treatment of acute liver injury (ALI; defined as aspartate transaminase [AST] > 200 IU/L or alanine transaminase [ALT] > 300 IU/L) might prevent progression to ALF and improve the outcome of patients with this condition[5]. Because early intervention for ALI/ALF might be beneficial, and prevention of the progression to ALF in ALI patients is possible, strict follow-up for early identification of ALI patients who satisfy the treatment indication is required. Because frequent follow up of all ALI patients is associated with increased human resources and medical costs in the hospital,[6, 7] it is important to identify patients with ALI that could likely progress to ALF and the markers that can predict disease progression.

To identify patients with ALI/ALF in our region, we have been working on a referral system for patients with ALI.[8-11] In this system, the Japan Hepatic Encephalopathy Prediction Model (JHEPM), which calculates age, etiology, serum total bilirubin (T-Bil), and PT, is used to evaluate the probability of coma development in patients with ALF. When the patients' JHEPM probability exceeds 20%, we recommend transferring them from the regional hospital to our hospital for intensive care.[8] Using

the JHEPM probability and the referral system, we can follow patients with ALI in our region and determine the prognosis of patients with ALI/ALF, regardless of whether they were transferred from the regional hospital to ours.

Models of end-stage liver disease (MELD) are widely used to assess the disease severity in patients with ALF.[12, 13] The MELD is calculated using T-Bil, serum creatine (Cre), and PT-INR, and it is useful to evaluate the appropriate timing for performing liver transplantation in patients with ALF.[12, 13] Therefore, the MELD score is a potential parameter to predict progression to ALF in ALI patients.

Patients are eligible for registration in our referral system if they present with ALI and have a prolonged PT value lower than 80% of PT activity. The patients were followed-up from registration until recovery of PT activity of up to 80% or more, or until progression to referral criteria or to ALF. By analyzing the follow up data compared with ALI outcome, we established a follow up strategy for ALI patients to predict the development of ALF.

Subjects and Methods

Subjects

Our database listed 365 consecutive patients who consulted our department for further evaluation of liver dysfunction between December 2007 and April 2016 (Figure 1). In the Introduction section, we briefly mentioned the inclusion criteria for registration in the database. The inclusion criteria were as follows: the absence of a diagnosis of either chronic hepatitis or liver cirrhosis, ALI (aspartate transaminase [AST] > 200 IU/L or alanine transaminase [ALT] > 300 IU/L), and prolonged PT (PT-INR > 1.2 or PT activity < 80%). After registration, laboratory data and physical findings were serially reported from regional hospitals. Although the doctors in the regional hospitals discussed treatment with the patients who were registered in the referral system with us, the doctor in the regional hospital made the final decision regarding the treatment of ALI. Because there is no gold standard strategy to treat ALI/ALF, the treatment of ALI/ALF in the present study varied. The number of patients with liver injuries due to hepatitis was 230, and 121 of these were excluded from the present study because they satisfied the criteria for ALF at the time of registration. A total of 109 patients who had ALI at registration were further analyzed. The details of the etiology of the liver disease in each patient are summarized in Table 1. Each etiology was diagnosed based on the criteria we described previously.[9, 10] All protocols reported in this study were approved by the Institutional Review Board of Iwate Medical University (approval number: H20-36).

Prediction models for coma development in ALF

The JHEPM probability was calculated for each patient based on the results of a biochemical examination and the reported etiology of liver failure at admission.[10] The formula is as follows: λ = [0.692 loge (1 + TBil (mg/dL))] − 0.065 PT (%) + [1.388 age (years)] + [0.868 etiology] − 1.156. In this formula, age has 1 point in patients older than 50 years, and etiology has 1 point when a non-acetaminophen-induced liver injury flared up due to type B hepatitis, autoimmune hepatitis (AIH), or unknown causes, and 0 points for other causes. The JHEPM value is calculated as follows: $p = 100/ (1 + e^{\lambda})$.

MELD

The MELD score was calculated using the following formula, based on the results of the hematological examination: MELD = 9.57 loge [Cre (mg/dL)] + 3.78 loge [T-Bil (mg/dL)] + 11.20 loge [PT-INR] + 6.43.

Laboratory data

Plasma PT and serum levels of ALT, AST, Cre, and T-Bil were determined by an autoanalyzer (JCA-BM2250, JEOL, Tokyo, Japan).

Statistical analysis

The results are expressed as the median value and range (minimum – maximum). All statistical analyses were performed using the SPSS 17.0 software program (SPSS Inc., Chicago, IL, USA). The chi-squared test, Student's t-test, and Mann-Whitney U test

were used to evaluate the statistical significance of the results. A two-sided p-value of <0.05 was considered statistically significant. A receiver operating characteristic curve (ROC) was used to assess the predictive performance of progression to ALF during observation. The cut-off values for progression to ALF were estimated by using the area under the ROC (AUROC) method. To identify factors that were associated with progression to ALF, a binomial logistic regression analysis and Cox hazard model were used.

Results

Subjects and laboratory findings:

A total of 109 patients were evaluated in the present study (Table 1). The average age was 49 years, and 53 patients were male. The etiologies of ALI varied among the patients; the most frequently reported were undetermined cause (30), drug-induced liver injury (23), and acute viral infection (18). Laboratory data revealed elevated transaminase level and mild coagulopathy.

Lower PT activity, higher JHEPM probability, higher MELD score, older age, and a higher incidence of AIH were observed in patients who progressed to ALF than in those who did not. To confirm the significance of these parameters, we compared the etiology and laboratory data at registration between these two groups (Table 2). Because not all patients in the present study satisfied the criteria for ALF at registration, the PT activity of the patients was above 40% of PT and below 1.5 of the PT-INR. However, the PT activity at registration was significantly lower in the patients who progressed to ALF than in those who did not [1.36 vs. 1.29 ($p<0.05$) and 61.1% vs. 66.0% ($p<0.05$), respectively]. The JHEPM probability and MELD score, as well as PT activity, also showed significant differences between the two groups [10.3% vs. 3.8% ($p<0.05$) and 12.8 vs. 10.3 ($p<0.05$), respectively]. Patients with progression were relatively older than those without [60.5 years old vs. 47.1 years old ($p<0.05$), respectively]. Regarding the etiology of ALI, we found that the incidence of AIH was significantly higher in the patients who progressed to ALF than in those who did not [22% vs. 7% ($p<0.05$), respectively].

Low PT activity and high JHEPM probability were significant risk factors for ALF progression in ALI patients. To investigate the significant risk factors for ALF progression in ALI patients, we used a multivariate analysis with binomial logistic regression and Cox hazard model using the following parameters: age, MELD score, T-Bil, JHEPM, AIH, and PT/PT-INR. PT activity and JHEPM were identified as significant risk factors associated with progression to ALF in ALI patients (Table 3 and supplemental table).

PT activity and JHEPM probability showed a high negative predictive value (NPV) of ALF progression in ALI patients. To determine if PT activity and JHEPM probability were predictive of progression to ALF, we evaluated the ROC of each parameter (Figure 2). PT activity and JHEPM probability showed a higher AUROC and higher sensitivity than the MELD score. To identify patients whose disease did not progress to ALF, we compared the NPV for disease progression. When 4.9%, 65% and 1.32 were used as cut-off values for JHEPM, PT, and PT-INR, respectively, the NPV of JHEPM, PT, and PT-INR was 0.910, 0.923 and 0.901, respectively.

Accuracy of JHEPM probability as a predictive parameter. Because we found that PT activity and JHEPM probability were useful to identify patients whose ALI did not progress to ALF, the accuracy of these parameters for prediction of progression was evaluated. The risk of progression to ALF was evaluated in terms of etiology, disease type, and prognosis (Table 4). JHEPM, PT, and PT-INR did not accurately predict the progression to ALF for 7, 4, and 7 patients, respectively. Drug-induced liver injury (DILI) was the most frequent etiology in both the JHEPM group and PT-INR group. In

1 the PT-INR group, the number of patients who died and those with ALF and coma was
2 higher. We evaluated number of the overestimated patients. JHEPM, PT-INR and PT
3 overestimated 11, 28 and 34 of the 82 patients with ALI, respectively.

Discussion

This prospective, observational study was performed in consecutive patients with ALI/ALF. In this setting, we identified that PT activity and JHEPM probability were predictive factors associated with progression from ALI to ALF, and the predictive ability of PT activity and JHEPM probability showed sufficient predictive performance. In particular, the NPV of these parameters was high. These data indicated that PT activity and JHEPM probability are useful to identify patients whose disease will not progress to ALF. Moreover, JHEPM probability, and PT and PT-INR values were useful for excluding patients who did not progress to ALF. The JHEPM probability might be an accurate predictive parameter to decide a follow-up strategy for ALI patients.

Hepatic encephalopathy occurs in ALF patients due to impairment of the biochemical function of the liver.[2] Once the biochemical function of the liver collapses, patients with ALF require intensive care in order to recover.[14] Recently, it has been reported that early intervention in ALI patients can reduce the risk of hepatic coma[5]. Based on these findings, strict follow-up of ALI patients is required for early detection of progression to ALF and check that these patients satisfy the indications for ALI treatment such as high-dose corticosteroid therapy.

PT activity is a sensitive parameter for protein synthesis, and it is therefore one of the criteria that determine ALF.[15-17] The present study demonstrated that PT activity was useful for identification of patients who did not progress to ALF. However, our detailed analysis of the characteristics of the patients who had their risk of disease progression underestimated using the PT activity, revealed that 4 of the 7 patients

assessed using PT-INR and 2 of the 4 patients assessed using PT died (Table 4). In contrast, 1 of the 7 patients assessed using JHEPM probability died. Furthermore, the death of the patient with an underestimated risk using JHEPM probability was not due to liver failure-related causes, but due to infection. In addition, the number of the overestimated patients by JHEPM probability is fewer compared with those by PT activity. These data indicate that JHEPM probability is a suitable parameter to identify patients whose disease does not progress to ALF. Based on these findings, we propose that patients who show a JHEPM probability of less than 4.9% might not need hospitalization for strict follow-up.

We focused on the etiology of ALF in the patients who had an underestimated risk by these parameters. Although the incidence of AIH was higher in the ALF group than in the ALI group, the incidence of DILI was higher in the patients in whom the risk of progression was underestimated by the JHEPM probability (3 of 7 patients) and PT-INR (3 of 7 patients). These data indicated that the disease severity of ALI due to DILI might not be exactly assessed at hospital registration. Indeed, previous studies have reported that patients with ALF due to DILI responded poorly to treatment.[11, 18, 19] Furthermore, liver dysfunction in patients with DILI-ALF occurs due to a different pathophysiology than that of AIH-ALF.[5, 11] Based on these findings and the present results, we speculate that DILI should be a focus when treating patients with ALI. When DILI is suspected as a cause of ALI, strict follow-up might be required.

This study has limitations that should be noted. First, there was no detailed evaluation on etiology because the number of the patients with each etiology was small.

Second, we also recognize the limitation associated with the usefulness of JHEPM as a predictive marker for the prognosis of ALF. Although JHEPM did not underestimate the deceased patients due to liver failure. There was no clinically significant difference between JHEPM and PT activity. To clarify the effect of each etiology and the clinical significance of JHEPM in the prediction of ALF development, a larger population of patients with ALI needs to be studied in future. Finally, the day of registration was not the same as the day that disease symptoms appeared. Therefore, data regarding the day of registration might be refluxed by different conditions during progression of disease.

The present study was a prospective observational study of consecutive patients. In this setting, predictive parameters of disease progression from ALI to ALF were identified. These findings might not only improve prognoses of ALI outpatients but also decrease the associated medical cost and human resources involved by reducing the need for frequent follow-up.

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Figure Legends

Figure 1. Flow chart of the patients who were eligible to participate in the present study

PT-INR: prothrombin time-international normalized ratio

Figure 2. The prediction of disease progression was analyzed with a receiver operating characteristic curve by using MELD, JHEPM, PT, and PT-INR.

The AUROC value was 0.617 for the MELD score, 0.739 for the JHEPM, 0.765 for PT, and 0.745 for PT-INR. The distinction of disease progression for sensitivity, specificity, positive predictive value, and negative predictive value was 0.630, 0.610, 0.347 and 0.833, respectively, for the MELD, 0.740, 0.866, 0.645 and 0.910, respectively, for the JHEPM, 0.852, 0.582, 0.404 and 0.923, respectively, for PT, and 0.740, 0.659, 0.417 and 0.901, respectively, for PT, and the cutoff values were 13.0 for the MELD, 4.9 for the JHEPM, 65.0 for PT, and 1.32 for PT.

AUROC: area under the receiver operating characteristic curve; JHEPM: Japanese Encephalopathy Prediction Model; MELD: models of end-stage liver disease; NPV: negative predictive value; PPV: positive predictive value; PT: prothrombin time; PT-INR: prothrombin time-international normalized ratio

Figure 1

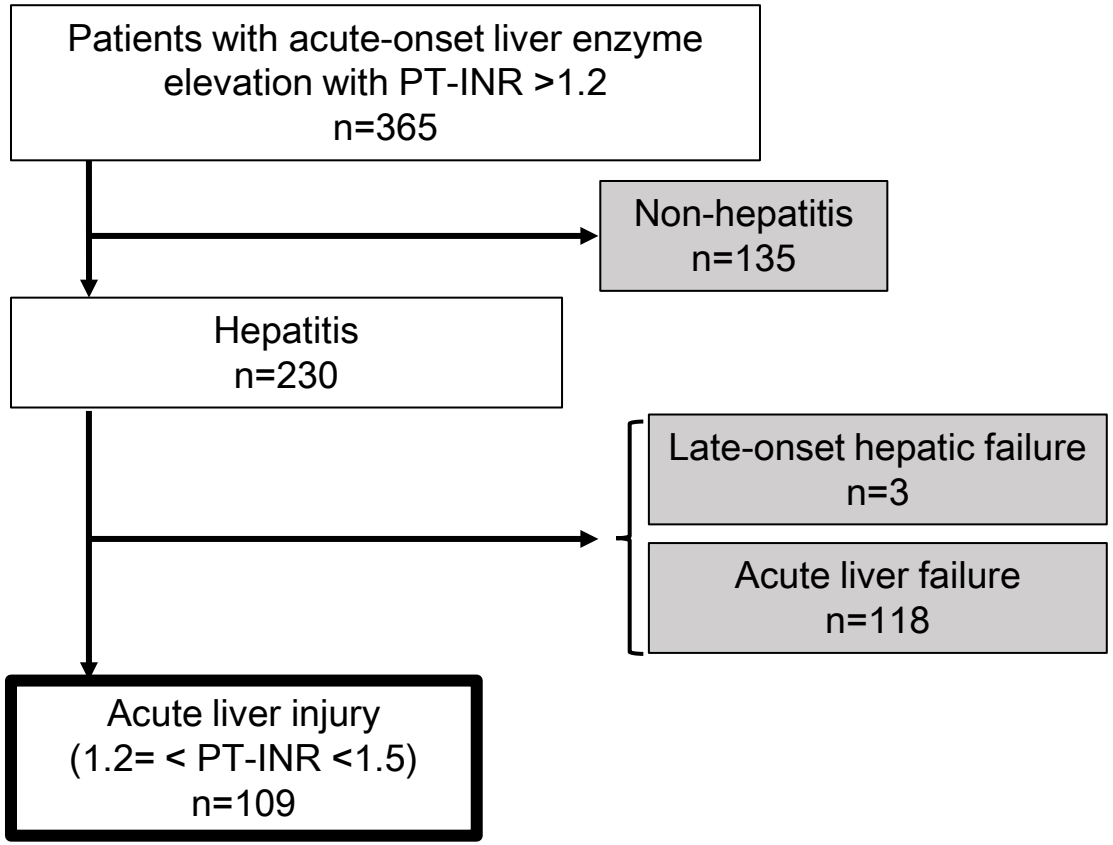
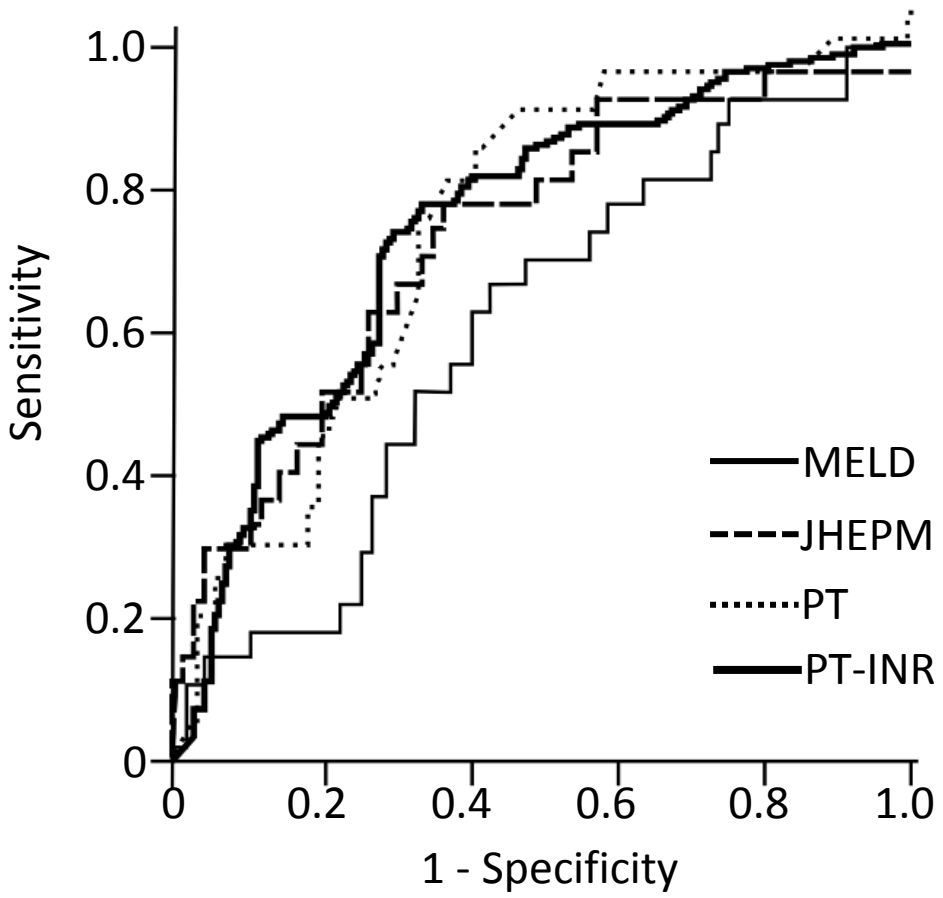

Patients with acute-onset liver enzyme elevation with PT-INR >1.2
n=365
Non-hepatitis
n=135
Hepatitis
n=230
Late-onset hepatic failure
n=3
Acute liver failure
n=118
Acute liver injury
(1.2= < PT-INR <1.5)
n=109

Figure 2



	AUROC	Cut-off value	Sensitivity	Specificity	PPV	NPV
MELD	0.617	13.0	0.630	0.610	0.347	0.833
JHEPM	0.739	4.9	0.740	0.866	0.645	0.910
PT(%)	0.765	65.0	0.852	0.585	0.404	0.923
PT-INR	0.745	1.32	0.740	0.659	0.417	0.901

1 Table 1. Patient characteristics

2

Age (years)	49 (range: 16-86)
Sex (M:F)	53: 56
Etiology	
Autoimmune	12
DILI	23
HBV acute	7
HBV carrier	10
HBV de novo	4
Other virus	18
Undetermined	30
Others	5
AST (U/L; mean, range)	990 (350-10763)
ALT (U/L; mean, range)	1191 (208-8150)
Cre (mg/dL; mean, range)	0.65 (0.10-2.10)
TBil (mg/dL; mean, range)	5.1 (0.3-38.2)
PT (%; mean, range)	64.3 (35-97)
PTINR (mean, range)	1.30 (1.20-1.48)
JHEPM (%; mean, range)	4.4 (0.1-52.5)
MELD score (mean, range)	12 (-8- 25)

Abbreviations: AIH: autoimmune hepatitis; ALT: alanine aminotransferase; AST: aspartate transaminase; Cre: creatinine; DILI: drug-induced liver injury; HBV: hepatitis B virus infection; JHEPM: Japan Hepatic Encephalopathy Prediction Model; MELD: model of end-stage liver disease; PT: prothrombin time; PT-INR: prothrombin time-international normalized ratio; TBil: total bilirubin.

1 Table 2. Characteristics of patients with acute liver injury and those with acute liver

2 failure

3

		ALI (n=82)	ALF (n=27)	p-value
Age (years; mean, range)		47.1 (31.0-66.0)	60.5 (45.8-70.3)	*, 0.015
Sex (M:F)		42:40	11:16	
ALI etiology, n (%)				
	AIH	6 (7)	6 (22)	*, 0.032
	DILI	17 (21)	6 (22)	
	HBV acute	6 (7)	1 (4)	
	HBV carrier	9 (11)	1 (4)	
	HBV de novo	3 (4)	1 (4)	
	Other viruses	11 (12)	7 (26)	
	Undetermined	26 (32)	4 (15)	
	Other	4 (5)	1 (4)	
Prognosis				
	Survive	82	27	
	Died		4	
T-Bil (mg/dL; mean, range)		5.2 (1.8-11.0)	8.9 (2.3-14.3)	
AST (U/L; mean, range)		772 (350-1352)	1133 (236-1703)	
ALT (U/L; mean, range)		1009 (436-1734)	1191 (285-1858)	

Cre (mg/dL; mean, range)	0.63 (0.50-0.80)	0.61 (0.50-0.81)	
PT-INR (mean, range	1.29 (1.24-1.36)	1.36 (1.30-1.40)	*, 0.01
PT (%; mean, range)	66.0 (61.3-71.0)	61.1 (52.4-64.8)	*, 0.02
JHEPM (%; mean, range)	3.8 (2.3-8.8)	10.3 (5.3-26.5)	*, 0.03
MELD score (mean, range)	10.3 (-8.0-25.0)	12.8 (3.0-23.0)	*, 0.045

*: $p<0.05$

Abbreviations: AIH: autoimmune hepatitis; ALF: acute liver failure; ALI: acute liver injury; ALT: alanine aminotransferase; AST: aspartate transaminase; Cre: creatinine; DILI: drug-induced liver injury; HBV: hepatitis B virus infection; JHEPM: Japan Hepatic Encephalopathy Prediction Model; MELD: model of end-stage liver disease; PT: prothrombin time; PT-INR: prothrombin time-international normalized ratio; TBil: total bilirubin.

Table 3 Risk of progression to acute liver failure from acute liver injury

Model 1	Odds ratio	95% CI	p-value
PT	0.93	(0.86-0.99)	0.017
JHEPM	1.05	(1.01-1.13)	0.025
Age	-		0.431
AIH	-		0.961
T-Bil	-		0.518
MELD	-		0.838
Model 2			
PT-INR	1.09*	(1.02-1.18)	0.013
JHEPM	1.07	(1.01-1.13)	0.021
Age	-		0.584
AIH	-		0.617
T-Bil	-		0.611
MELD	-		0.827

*: Incremental odds ratio for 0.01 increases PT-INR.

Abbreviations: AIH: autoimmune hepatitis; CI: confidence interval; JHEPM: Japan Hepatic Encephalopathy Prediction Model; MELD: model of end-stage liver disease; PT: prothrombin time; PT-INR: prothrombin time-international normalized ratio; TBil: total bilirubin.

1 Table 4 Detailed characteristics of the patients with ALF whose risk of ALF progression

2 was underestimated, using the cut-off value

3

Age	Sex	Etiology	Disease	Prognosis	Cause of death	JHEPM	PTINR	PT
74	F	Others	ALF without coma	Deceased	ARDS	0.1 ×	1.23×	77.0 ×
41	F	DILI	ALF without coma	Survive		1.4 ×	1.32×	60.1
42	F	Other virus	ALF without coma	Survive		2.9 ×	1.36	50.3
18	F	Other virus	ALF without coma	Survive		3.1 ×	1.39	52.4
43	F	DILI	ALF without coma	Survive		3.4 ×	1.35	64.0
50	F	DILI	ALF without coma	Survive		3.7 ×	1.39	50.7
69	F	Other virus	ALF without coma	Survive		4.9 ×	1.41	62.8
68	M	HBV de novo	ALF with coma, subacute type	Deceased	Coagulo pathy	5.1	1.26 ×	69.0 ×
71	M	Other virus	ALF without coma	Survive		7.6	1.22 ×	63.4
71	F	DILI	ALF with coma, subacute type	Deceased	Coagulo pathy	11.8	1.27 ×	63.5
61	F	HBV carrier	ALF without coma	Survive		15.2	1.21 ×	75.0 ×
57	F	DILI	ALF without	Deceased	ARDS	23.9	1.30 ×	50.0

75	M	Autoimmune	coma ALF without coma	Survive	31.4	1.35	66.0	×

"×" was indicated as subject who was underestimated by indicated factors.

Abbreviations: AIH: autoimmune hepatitis; ALF: acute liver failure; ARDS: acute respiratory distress syndrome; DILI: drug-induced liver injury; HBV: hepatitis B virus infection; JHEPM: Japan Hepatic Encephalopathy Prediction Model; MELD: model of end-stage liver disease; PT: prothrombin time; PT-INR: prothrombin time-international normalized ratio.

Supplemental table. Risk of progression to acute liver failure from acute liver injury analyzed by Cox hazard model.

	Hazard ratio	95% confidence interval	p value
PT-INR	359.4	1.90-75194.65	0.028
JHEPM	1.04	1.00-1.09	0.035
MELD	1.01	0.92-1.10	n.s.
Age	0.99	0.97-1.03	n.s.
AIH	-		n.s.
T-Bil	-		n.s.
MELD	-		n.s.

	Hazard ratio	95% confidence interval	p value
PT	0.95	0.90-0.99	0.031
JHEPM	1.06	1.01-1.11	0.025
MELD	0.98	0.91-1.07	n.s.
Age	1.01	0.98-1.03	n.s.
AIH	-		n.s.
T-Bil	-		n.s.
MELD	-		n.s.

Abbreviations: JHEPM: Japan Hepatic Encephalopathy Prediction Model; MELD: model of end-stage liver disease; PT: prothrombin time; PT-INR: prothrombin time-international normalized ratio.