A Predictive Formula for Acute Liver Failure is Useful for Predicting the Prognosis of Patients with Acute-on Chronic Liver Failure

Keisuke Kakisaka [1)]

Kojiro Kataoka [1)]

Hidekatsu Kuroda[1)]

Yasuhiro Takikawa [1)]

1) Division of Hepatology, Department of Internal Medicine,

Iwate Medical University,

Morioka, Japan

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Address for correspondence: Keisuke Kakisaka, M.D., Ph.D.

School of Medicine

Iwate Medical University

19-1 Uchimaru Morioka

Iwate, JAPAN 0208505

Tel.: +81-19-651-5111

Fax: +81-19-652-6664

E-mail: keikaki@iwate-med.ac.jp

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Abbreviations: Acute on chronic liver failure (ACLF), acute liver failure (ALF), model for end-stage liver disease (MELD), hepatic encephalopathy (HE),Japan HE prediction model (JHEPM), aspartate transaminase (AST), alanine aminotransferase (ALT), prothrombin time activity (PT), prothrombin time-international normalized ratio (PT-INR), alpha fetoprotein (AFP), albumin (Alb), creatinine (Cre), hepatic growth factor (HGF), total bilirubin (Tbil), receiver–operator curve (ROC), area under the receiver operating characteristic curve (AUROC), autoimmune hepatitis (AIH), alcoholic liver disease (ALD), viral hepatitis B virus infection (HBV).

Abstract: **Background & aim**: The prognosis of acute-on chronic liver failure (ACLF) is extremely poor in comparison to acute liver failure (ALF). We aimed to establish methods for the early diagnosis of ACLF and its severity to identify the patients with a poor prognosis. **Methods:** The laboratory data at admission of 30 ACLF and 46 ALF patients were compared. Three established prognosis prediction models (model for end stage liver disease [MELD]; MELD modified by serum sodium concentration, [MELD-Na]; and the Japan hepatic encephalopathy prediction model [JHEPM]) were assessed using area under the receiver operating characteristic curve (AUROC) values. **Results:** No significant difference was found in the laboratory data of the two patient groups. J-HEPM was able to predict the outcome of the ACLF subjects (AUROC, 0.93). **Conclusions:** Although ACLF could not be differentially diagnosed from ALF at admission from the laboratory data alone, the JHEPM effectively predicted the prognosis of liver failure in patients with ACLF. These findings indicate that ACLF patients with high J-HEPM scores require earlier and more intensive care than ALF patients.

Introduction:

Liver failure is characterized by coagulopathy, impaired detoxification and impaired protein synthesis[1]. “Acute liver failure” (ALF) is the term used to describe a liver injury caused by acute insults without the presence of chronic liver disease[2]. The term, “acute-on chronic liver failure” (ACLF) is used to describe a liver injury in which the underlying cause is chronic liver disease[3]. The acute presentation of ACLF may be difficult to distinguish from ALF without any histological findings of chronic liver disease.

Several prediction models for the prognosis in ALF have been reported. In particular, the model for end-stage liver disease (MELD) and MELD modified by serum sodium concentration (MELD-Na) are well-known as useful models for this purpose[4, 5]. Furthermore, the authors have established the Japan hepatic encephalopathy (HE) prediction model (JHEPM) for ALF, and examined the clinical significance of the HE prediction model in the prevention of HE development through early intervention in patients with acute liver injury[6]. It is generally noticed that mortality is higher in ACLF than in ALF[3, 7-9]. An accurate diagnosis of ACLF

in the acute phase of liver failure will provide a chance for earlier and more adequate treatment, and may contribute to decreasing the mortality associated with the disease, which may extend to a new therapeutic strategy for ACLF.

The most common underlying chronic liver diseases in cases of ACLF are non-alcoholic steatohepatitis, chronic hepatitis and cirrhosis. **In general,** chronic liver disease before ACLF development are well compensated and thus may show no symptoms [3]. The diagnosis of ACLF without any information about chronic insults is therefore difficult to diagnose at the acute phase and is usually retrospectively determined using clinical history, clinical course, histology or imaging.

The acute insults associated with liver injury in ACLF are alcoholic drinking, viral hepatitis infections, autoimmune disease, Wilson's disease and drug-induced liver injury[3]. If ACLF could be diagnosed at its acute phase and features of the clinical course that are specific to ACLF could be found, these findings would provide a better understanding of the pathophysiology of the disease. In addition, collecting the clinical data of ACLF patients with a poor prognosis may contribute to the understanding of the pathophysiology

of ACLF in patients with a poor prognosis.

The aims of the present study were as follows: (1) to differentiate ACLF at its acute phase from ALF in laboratory data; (2) to confirm the prediction parameters for poor prognosis in ACLF patients; and (3) to confirm the clinical aspects and etiology of each case of ACLF during hospitalization. The present study suggested that: (1) ACLF in its acute presentation was not distinguishable from ALF at admission, (2) the JHEPM, but not the MELD score or the MELD-Na score, was able to predict prognosis of liver failure in patients with ACLF using both the patient's preceding and current conditions, and (3) the causes of death in ACLF differ according to the etiology of the underlying chronic disease.

Subjects and Methods:

Subjects: A total of 540 patients who consulted to our department for the further evaluation of liver dysfunction between 2006 and 2013 were listed in our database. The inclusion criteria for registration to the database were as follows: the absence of a diagnosis of either chronic hepatitis or liver cirrhosis, an acute liver injury (aspartate transaminase [AST] >200 IU/L or alanine transaminase [ALT] >300 IU/L) and a prolonged prothrombin time (prothrombin time-international normalized ratio [PT-INR] >1.2 or prothrombin time activity [PT] <80%)[6, 10]. During treatment or observation after registration in the list, 182 of the patients were found to meet the definition of either ACLF or ALF. Liver failure in ACLF was defined as a liver injury in a patient without history of ascites, jaundice or hepatic encephalopathy, a PT-INR of > 1.5 during hospitalization and jaundice (serum bilirubin >5 mg/dL)[3]. The underlying chronic liver insults of the ACLF were diagnosed by oral query about chronic hepatitis, radiological imaging, the presence of elevated of fibrosis markers or from histological findings. ALF was defined as liver injury in a patient with no known previous liver disease, a PT-INR of > 1.5 during

hospitalization, and an illness of < 24 weeks in duration[11, 12]. One hundred and six of these subjects were excluded from the study for various reasons, including complications associated with disseminated intravascular coagulopathy or a lack of serum data or blood samples. After applying the exclusion criteria, the subjects with liver failure in ACLF (n=30) and the subjects with ALF (n=46) were included in the study (Figure 1). The details of the etiology of the liver disease in each of the subjects is summarized in Table 1. Thus, the laboratory data of some of the patients who presented with ACLF or ALF at admission meant that they did not meet the inclusion criteria for the study.

All of the protocols reported in this paper were approved by the Institutional Review Board of Iwate Medical University (approval number: H20-36).

Laboratory data: The plasma PT-INR value, PT time and serum levels of alpha-fetoprotein (AFP), albumin (Alb), ALT, AST, creatinine (Cre), hepatocyte growth factor (HGF) and total bilirubin (Tbil) were analyzed using an autoanalyzer (JCA-BM2250, JEOL, Tokyo, Japan).

In order to compare the PT-INR value during hospitalization, the

period of 7 days around discharge was defined as “late” period. The maximum value of PT-INR during hospitalization was defined as the “Peak PT-INR value.”

Evaluation of prognostic models for ACLF: The MELD-Na, MELD, and JHEPM scores were calculated for each patient based on the results of a hematological examination and the reported etiology of liver failure on admission. The detailed formulas that were used are as follows:

MELD = 9.57 loge [Cre (mg/dL)] + 3.78 loge [Tbil (mg/dL)] + 11.20 loge [PT-INR] + 6.43,

MELD-Na = MELD – Na – [0.025 × MELD × (140 – Na)] + 140,

JHEPM = [0.692 loge (1 + Tbil (mg/dL))] - 0.065 PT(%) + [1.388 Age(years)] + [0.868 Etiology] - 1.156; where Age is 1 in patients older than 50 years and Etiology is 1 when the cause of a non-acetaminophen-induced liver injury is flare-up of type B hepatitis, auto-immune hepatitis or unknown, and 0 for other causes[6]. J-HEPM value is calculated as follows; $p = 100/(1 + e^{-\lambda})$.

The predictive performance for prognosis of the MELD-NA and MELD scores and of the J-HEPM was assessed in patients with

ACLF-related liver failure using the receiver–operator curves (ROC) method. The cut-off values for early prediction of poor prognosis were estimated using the area under the ROC (AUROC) method.

Statistical analysis: The results are expressed as the mean and standard deviation or median and 25-75 percentile according to the distribution. All statistical analyses were performed using the SPSS 17.0 software program (SPSS Inc., Chicago, IL, United States). Non-parametric tests (Kruskal-Wallis followed by Dunn's multiple comparisons) were used to evaluate the statistical significance of the results. A two-sided p value of <0.05 was considered to be statistically significant. Spearman's correlation was used to assess the statistical significance of the correlations.

Results:

Clinical characteristics of the ACLF and ALF patients with liver failure: According to the summary of the patient characteristics, both AIH and HBV infection in patients with ACLF, and both HBV infection and DILI in patients with ALF, were associated with poor prognosis (Table 1). The mortality of patients with ACLF was higher than that of patients with ALF (Table 1). To confirm the clinical aspects of ACLF at admission, the laboratory data of the patients with ACLF were compared to the data of the patients with ALF. The serum AST and ALT values were found to be significantly higher in the patients with ALF than in the patients with ACLF (Table 2). In contrast, there were no differences between the two groups in the levels of plasma prothrombin and serum albumin. Although the AFP level would indicate the induction of liver regeneration in the damaged liver, it did not differ between the two groups [13]. Importantly, there was no difference between the two groups in the results of any of the prognostic models: the MELD score, the MELD-Na score or the J-HEPM (Table 2). These data indicated that it was not possible to differentiate ACLF from ALF solely through the use of the laboratory data on admission.

The Japan HE prediction model predicted the prognosis of the ACLF patients with liver failure: Given that the liver failure in the ACLF cases was not distinguishable from ALF using the laboratory data on admission, we next focused on the reasons for the poorer prognosis of ACLF. To clarify the clinical aspects of the deceased patients with ACLF, we compared the laboratory data of the deceased patients with the data of the surviving patients in the ACLF group. The serum creatinine and AST levels were higher in the surviving patients than they were in the deceased patients (Table 3). Although there were no differences in the MELD-NA or MELD scores of the deceased and surviving patients, the J-HEPM score was significantly higher in the deceased patients (Figure 2A, B and C). The AUROC value of the J-HEPM for predicting mortality was 0.930 (Figure 3).

Although the MELD-Na and MELD scores have previously been reported to be good prediction models for the prognosis of ACLF, they did not predict prognosis in the subjects of the present study (Figure 3). To clarify the reason for their low predictive effect, we investigated the PT-INR Tbil and creatinine levels to determine which of the levels showed the greatest contribution to the increase of the two score system. In the deceased patients,

both the MELD-Na and the MELD scores correlated with the PT-INR (Figure 4A and C). In contrast, these scores were correlated with the serum creatinine level in the surviving patients (Figure 4B and D). The serum total bilirubin level was not correlated with the MELD-Na or MELD scores in either of the patient groups (data not shown). No differences were observed in the MELD-Na or MELD scores for any of the etiologies (Figure 2B and C). These data indicated that the scores of both systems increased in the deceased patients in association with PT prolongation. In contrast, the increased scores of the surviving patients were associated with an elevation of creatinine levels. Put simply, the high MELD-Na or MELD scores in the deceased patients were due to liver failure (PT prolongation), while the high scores in the surviving patients were due to renal failure (creatinine level increase).

Advanced age in patients with AIH-ACLF and coagulopathy in alcoholic ACLF as perturbing factors for JHEPM: According to the ROC of the J-HEPM for predicting prognosis, a value of 35, which was calculated as probability of development of hepatic encephalopathy (see "Subjects and Methods"), was calculated using the Youden index (Figure 3). During our

evaluation of the accuracy of the J-HEPM in predicting prognosis for each etiology, we found that the value for survival of ACLF from AIH was high and that the value for ACLF from alcoholic hepatitis was only appropriate in some patients (Figure 2A). The age of all subjects with ACLF from AIH was >50 years, whereas the subjects with alcoholic ACLF were 46.5 years of age, and those with HBV-related ACLF were 46.9 years of age (Table 1). Because the J-HEPM was calculated using age, etiology, prothrombin time and total bilirubin, a high age value resulted in high prediction model value. This was the reason for the high value that was found for ACLF from AIH (Table 4). Next, we considered the reasons why the values were inappropriate for some of the cases of ACLF from alcoholic hepatitis. In this case, we hypothesized that the sensitivity of prothrombin time to the severity of ALF might make the parameter unsuitable for predicting the severity of liver failure in ACLF from alcoholic hepatitis. To confirm our hypothesis, the PT-INR value was serially observed in ACLF patients. In the surviving ACLF patients, PT-INR recovered toward discharge (Figure 5). In contrast, the PT-INR peaked at the late phase of the clinical course in the deceased ACLF patients, except for those with alcoholic hepatitis (Figure 5). Interestingly, in patients with

ACLF from alcoholic hepatitis, the PT-INR value in the late phase was lower than the peak PT-INR value, despite the fact that these patients did not receive coagulation factor supplementation. Furthermore, in 4 of the 5 deceased patients with ACLF from alcoholic hepatitis, a complication of spontaneous bleeding from the soft tissue was reported, which led to a poor prognosis. In fact, 2 of the 5 deceased patients showed spontaneous bleeding into the iliopsoas muscle, while the other 2 showed a non-variceal hemorrhage from other organs. These data indicated that the ACLF based on alcoholic hepatitis had consistent coagulopathy, which might be associated with advanced chronic hepatitis or liver cirrhosis.

Discussion: ACLF is an emergent problem because its intractability results in high mortality[7, 14, 15]. Multiple organ failure, compensatory anti-inflammatory response syndrome and severe infection are considered to be the main causes of death in ACLF patients[16-18]. Based on these considerations, several models to predict the prognosis of ACLF have been proposed. The MELD score has been reported to be a useful prediction model for ACLF based on HBV infection[14, 19]. The SOFA score would be considered to be a good prediction model when ACLF is complicated by a critical illness associated with organ failure or severe infection[20, 21]. However, there has been no uniform prediction model for liver failure in ACLF patients. Interestingly, the J-HEPM was capable of predicting the deceased patients in the study (Figure 3). Given that the ACLF patients in the present study either presented with conditions preceding liver failure or with liver failure, the results in the present study could be said to provide evidence that, in clinical settings, the current model is useful for predicting the prognosis of ACLF patients with liver failure.

According to the finding of serial changes in the serum creatinine level in the present study, renal dysfunction in the ACLF patients was

considered to be a transient and reversible condition, which did not lead to a poor prognosis. The high MELD score, which was derived from the high creatinine level, therefore overestimated the severity of the condition of the surviving ACLF patients. Hyperbilirubinemia, which is caused by liver failure in ACLF patients, also elevates the MELD score. The patients with hyperbilirubinemia showed a high MELD score and was associated with poor prognosis. The same tendency was found in the MELD-Na score. Taken together, high MELD scores were found for two groups of patients in the present study: the high serum creatinine group, and the hyperbilirubinemia group. Given that thes groups both showed different prognoses, the MELD and MELD-Na scores were not considered to be capable of predicting prognosis in the present study.

In the present study, the underlying chronic liver diseases in the ACLF patients included alcohol, autoimmune hepatitis and HBV infection. In deceased patients with ACLF from AIH or HBV infection, the peak PT-INR value occurred in the “late” period (close to the time of discharge). These data indicate that these patients demonstrated progressive coagulopathy, which might be associated with liver failure. In contrast, some

patients with ACLF from alcoholic hepatitis demonstrated consistent coagulopathy (Figure 5). Indeed, all of the deceased patients with ACLF from alcoholic hepatitis died as a result of uncontrollable bleeding. Previous reports have indicated that alcoholic liver cirrhosis is associated with a high risk of intramuscular bleeding and that the suspected causes of bleeding were the promotion of arteriosclerosis and impaired platelet adhesion to fibrinogen[22-25]. Although the detailed mechanism behind the uncontrollable bleeding remains unclear in the present cases, a weakening of the vascular wall and coagulopathy are the suspected causes. We hypothesize that an understanding of the bleeding mechanism might help us to prevent such bleeding and to improve mortality in patients with ACLF from alcoholic hepatitis.

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FIGURE LEGENDS

Figure 1. Flowchart of the subject selection process. Abbreviations: acute liver failure ALF; acute on chronic liver failure, ACLF.

Figure 2. The Japan HE prediction model demonstrated high scores in deceased patients with ACLF. The horizontal axes show prognosis and each of the etiologies in graphs showing (A) the J-HEPM (Japan HE prediction model), (B) MELD-Na and (C) MELD. Closed circles indicate the deceased patients. Open circles indicate the surviving patients.

Figure 3. The Japan HE prediction model showed high accuracy in predicting prognosis in ACLF patients with liver failure. The area under the ROC (AUROC) values of the prognosis in the subjects were 0.885 for the Japan HE prediction model (J-HEPM), 0.481 for the MELD-Na and 0.524 for the MELD. Solid line, the J-HEPM; dashed line, the MELD-Na score; dotted line, the MELD score.

Figure 4. Correlation of each of the parameters to either the MELD-Na or MELD scores. The correlations of each of the parameters to the MELD score are presented in graphs A and B. The horizontal axes show the MELD scores, while the vertical axes show the parameters for (A) PT-INR

and (B) serum creatinine (Cre). The correlation of each of the parameters to the MELD-Na score is shown in C and D. Closed circles indicate the deceased patients. Open circles indicate the surviving patients. All correlations were analyzed using Spearman's correlation.

Figure 5. Peak PTI-INR and late-phase PT-INR in ACLF patients. The horizontal axis shows the peak PT-INR value. The vertical axis shows the late-phase PT-INR value. "Late-phase" was defined as the period of 7 days around the time of discharge. Open symbols show the surviving patients. Closed symbols show the deceased patients. Diamonds show patients with ACLF from autoimmune hepatitis (AIH), squares show patients with ACLF from alcoholic hepatitis (AL) and triangles show patients with ACLF from hepatitis B virus infection (HBV).

Figure 1.

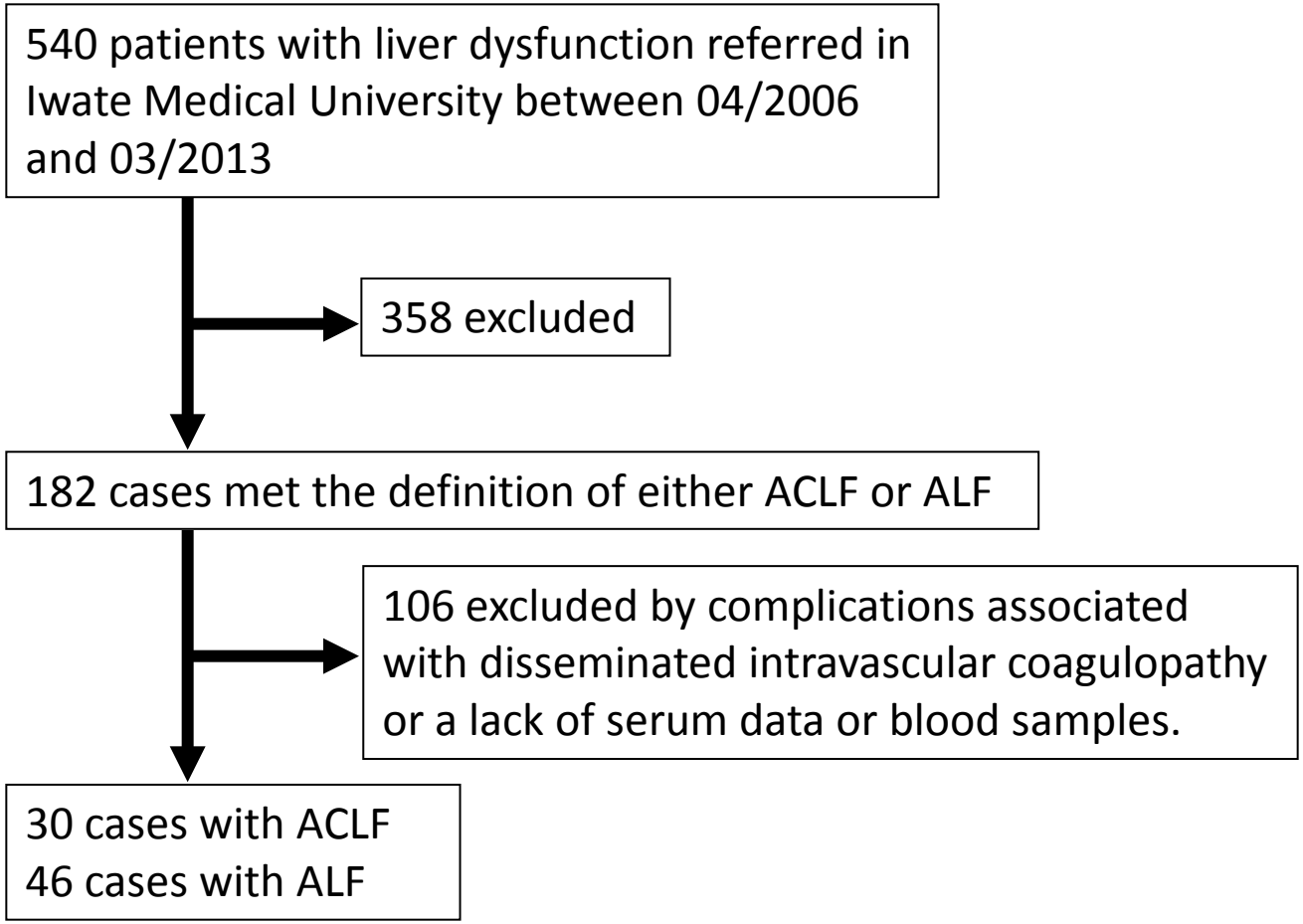
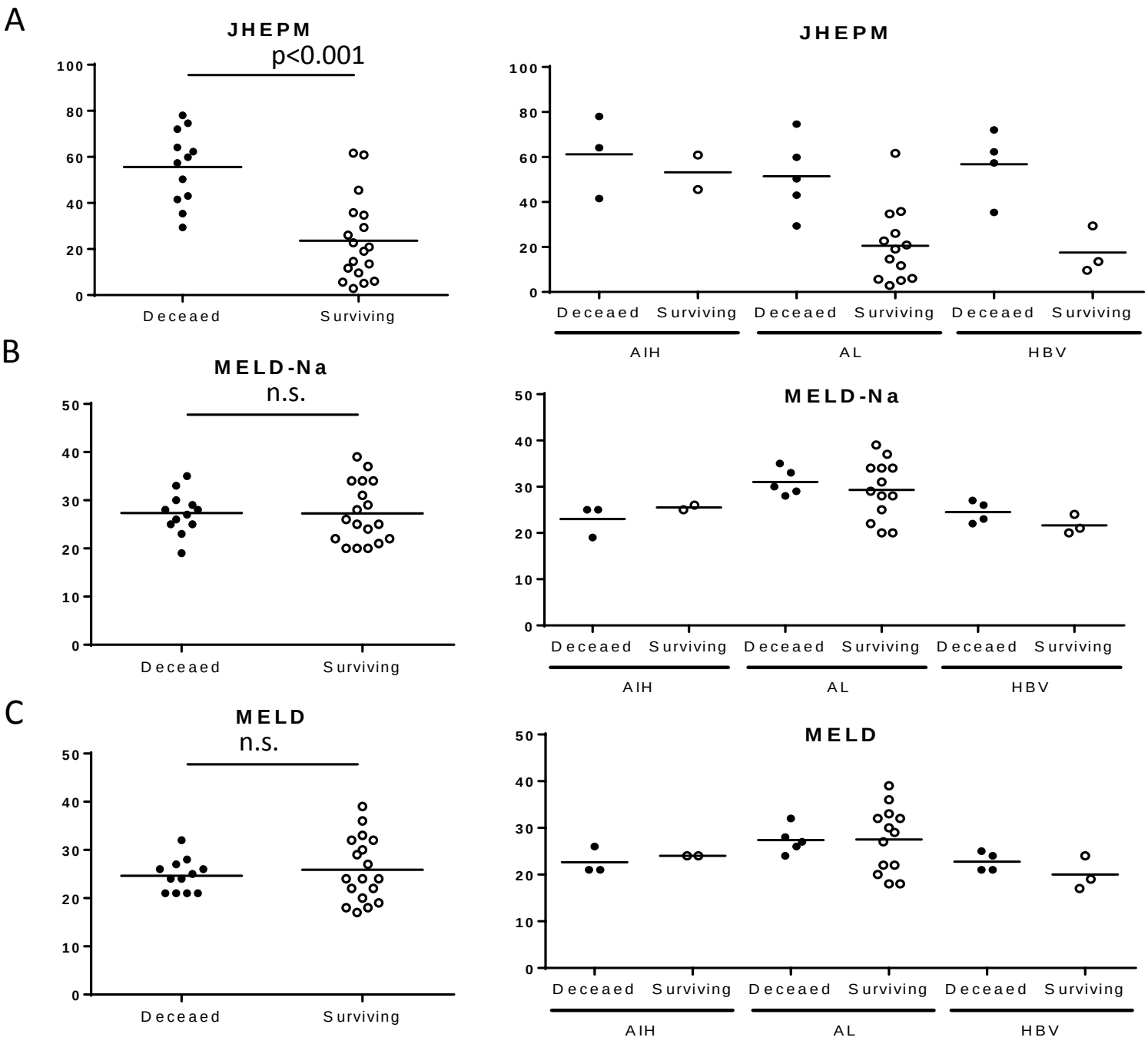

540 patients with liver dysfunction referred in Iwate Medical University between 04/2006 and 03/2013
358 excluded
182 cases met the definition of either ACLF or ALF
106 excluded by complications associated with disseminated intravascular coagulopathy or a lack of serum data or blood samples.
30 cases with ACLF
46 cases with ALF

Figure 2


A
JHEPM
p<0.001
100
80
60
40
20
0
Deceaed
Surviving
JHEPM
Deceaed
Surviving
Deceaed
Surviving
Deceaed
Surviving
AIH
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HBV
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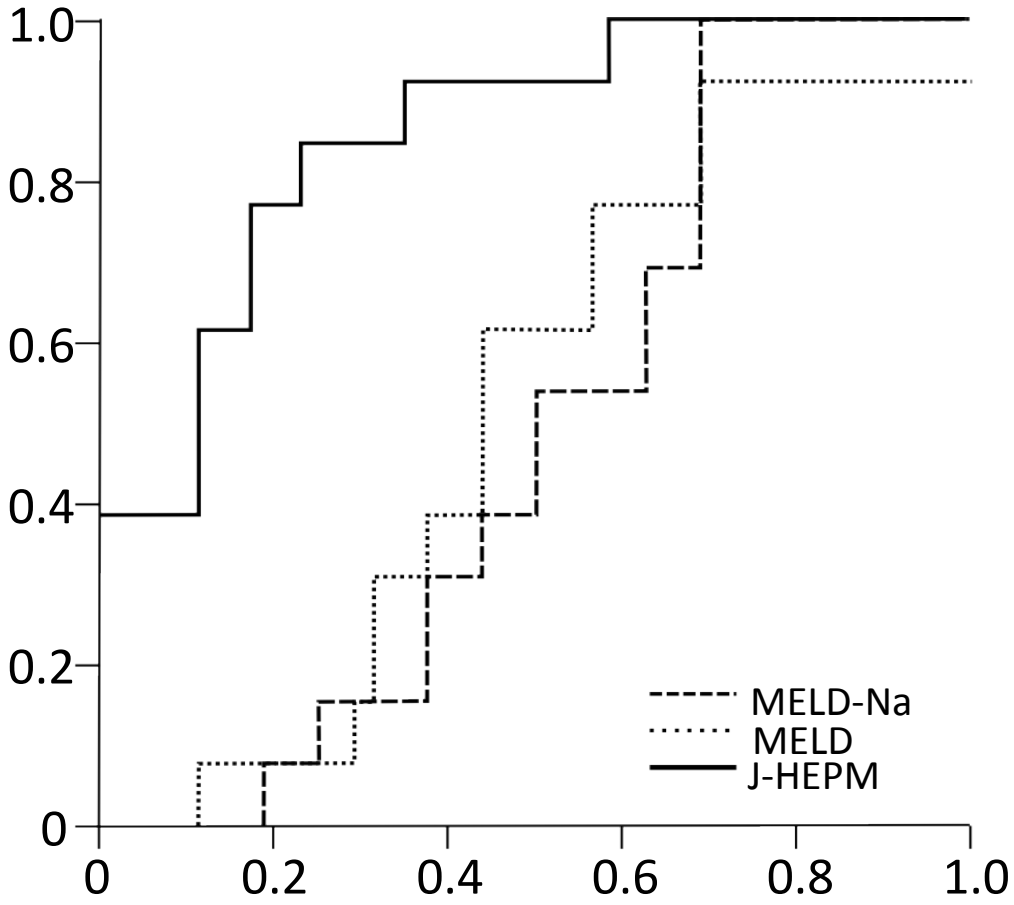
AL
HBV

Figure 3



	AUROC	p value
J-HEPM	0.930	0.001
MELD-Na score	0.438	0.624
MELD score	0.438	0.624

Youden index
=35.060

Cut off value (J-HEPM)	35.060
Sensitivity	0.852
Specificity	0.846
Positive predictive value	0.920
Negative predictive value	0.733

Figure 4

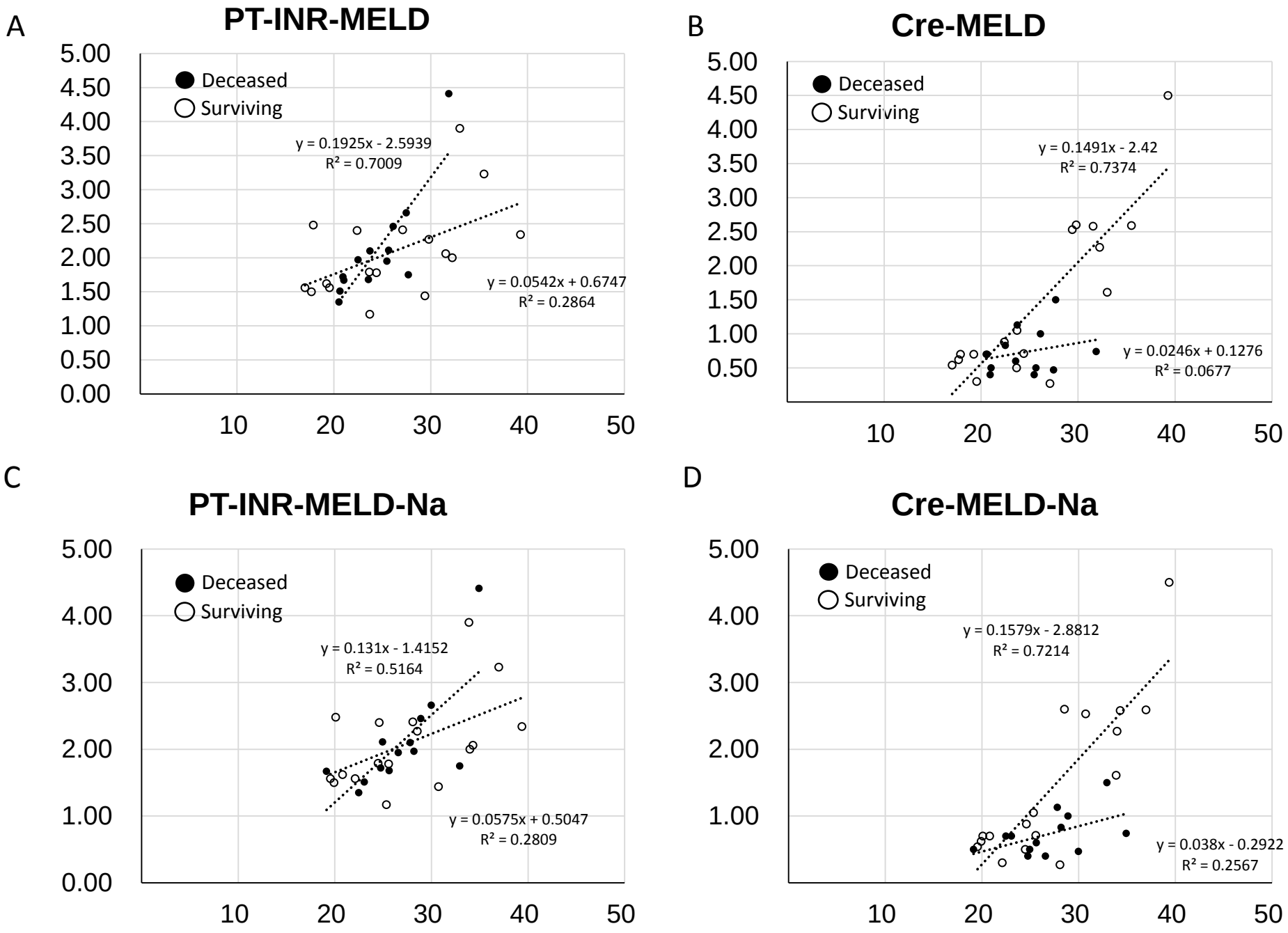

A
PT-INR-MELD
Deceased
Surviving
y = 0.1925x - 2.5939
R² = 0.7009
y = 0.0542x + 0.6747
R² = 0.2864
B
Cre-MELD
Deceased
Surviving
y = 0.1491x - 2.42
R² = 0.7374
y = 0.0246x + 0.1276
R² = 0.0677
C
PT-INR-MELD-Na
Deceased
Surviving
y = 0.131x - 1.4152
R² = 0.5164
y = 0.0575x + 0.5047
R² = 0.2809
D
Cre-MELD-Na
Deceased
Surviving
y = 0.1579x - 2.8812
R² = 0.7214
y = 0.038x - 0.2922
R² = 0.2567

Figure 5.

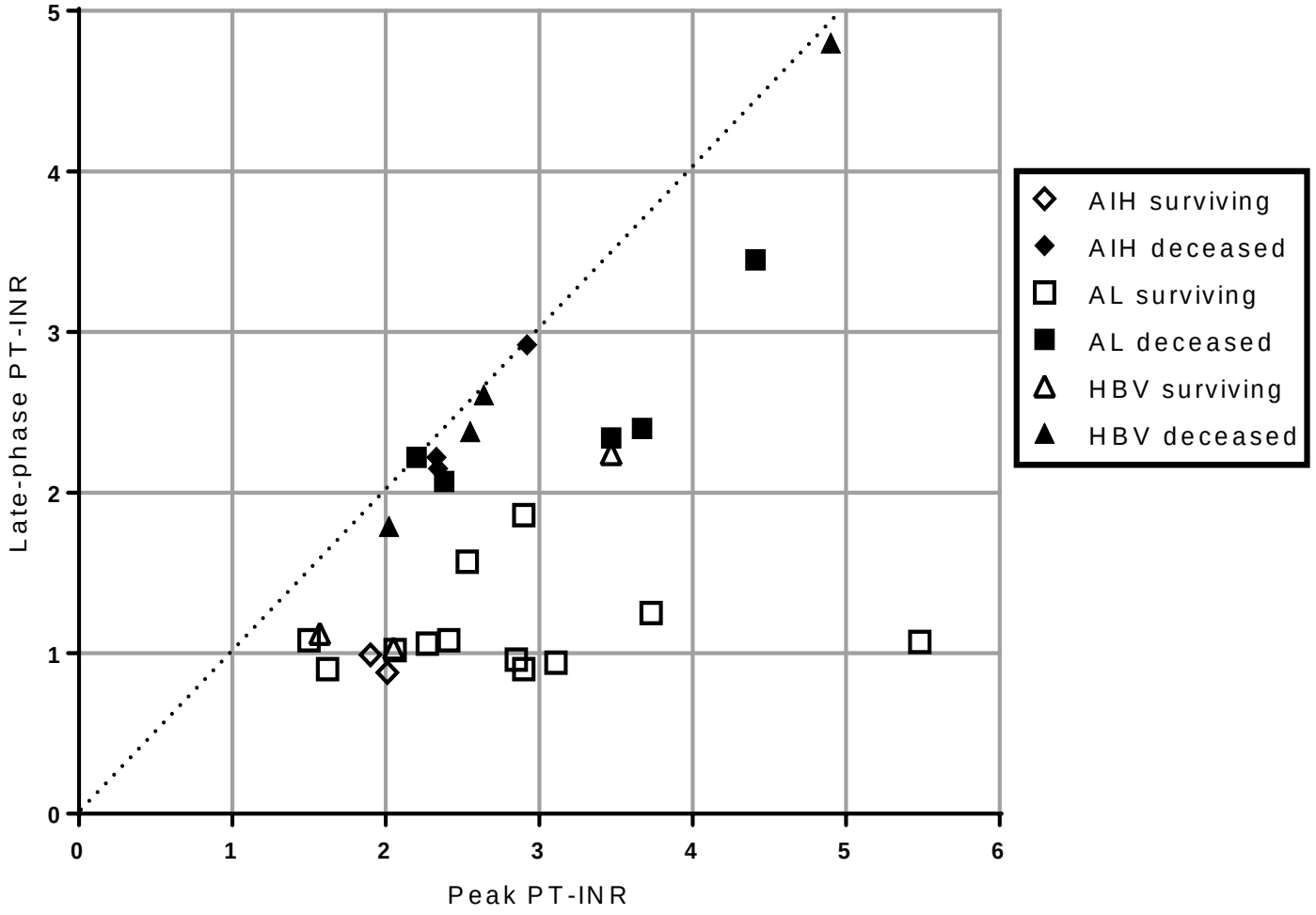

Late-phase PT-INR
Peak PT-INR
0
1
2
3
4
5
6
AIH surviving
AIH deceased
AL surviving
AL deceased
HBV surviving
HBV deceased

Table 1. Etiologies of acute-on chronic liver failure (ACLF) and acute liver failure (ALF) in 76 subjects

ACLF

Etiology		Age (y.o.)	Female: Male	Deceased	Mortality (%)
AIH	(5)	77.8 ± 0.9	5:0	3	60
AL	(18)	46.5 ± 2.8	10:8	5	28
HBV	(7)	46.9 ± 4.2	1:6	4	57
Total	(30)	51.8 ± 2.9	16:14	12	40

ALF

Etiology	Age (y.o.)	Female: Male	Type of disease			HE (≥ grade II)	Deceased	Mortality (%)
			coma (-)	coma (+), acute	coma (+), subacute			
AIH (6)	64.8 ± 2.2	3:3	6	0	0	0	0	0
DILI (7)	67.1 ± 4.0	4:3	4	0	3	3	4	57
HBV (9)	52.4 ± 4.1	4:5	5	1	3	4	4	44
Others (24)	50.6 ± 4.1	16:8	20	3	1	4	4	17
Total (46)	55.4 ± 2.5	27:19	35	4	7	11	12	26

Acute-on chronic liver failure, ACLF; autoimmune hepatitis, AIH; alcoholic hepatitis, AL; acute liver failure, ALF; drug-induced liver failure, DILI; hepatitis B virus infection, HBV; hepatic encephalopathy, HE.

Table 2. Laboratory data and the prediction models for acute-on chronic liver failure (ACLF) and acute liver failure (ALF)

		ACLF			ALF			
		Average		SD	Average		SD	
J-HEPM		36.0	±	23.6	39.4	±	24.3	n.s.
MELD-Na score		25.4	±	5.6	23.6	±	7.2	n.s.
MELD score		27.2	±	5.5	25.4	±	7.0	n.s.
Alb	mg/dL	2.8	±	0.2	3.1	±	0.6	n.s.
Cre	mg/dL	1.15	±	0.18	0.95	±	0.21	n.s.
Tbil	mg/dL	11.0	±	5.6	10.7	±	10.6	n.s.
AST	IU/L	1101	±	1393	2338	±	2979	$p<0.05$
ALT	IU/L	845	±	897	2226	±	2139	$p<0.05$
AFP	ng/mL	86.8	±	219.0	100.4	±	306.8	n.s.
HGF	ng/mL	2.0	±	1.6	2.7	±	3.6	n.s.
Plt	10^4/mL	14.1	±	2.6	14.7	±	1.2	n.s.
APTT	sec.	46.4	±	2.9	69.6	±	15.2	n.s.
PT	%	37.4	±	2.6	35.1	±	2.47	n.s.
PT-INR		2.10	±	0.13	2.48	±	0.24	n.s.

Acute-on chronic liver failure, ACLF; alpha fetoprotein, AFP; albumin, Alb; acute liver failure, ALF; alanine aminotransferase, ALT; aspartate aminotransferase, AST; APTT, activated partial thromboplastin time; creatinine, Cre; hepatocyte growth factor, HGF; Japan HE prediction model, J-HEPM; model for end-stage liver disease, MELD; MELD-Na, MELD modified by sodium concentration; platelet, Plt; prothrombin time, PT; PT-INR, PT-international normalized ratio; standard deviation, SD; total bilirubin, Tbil

Table 3. Laboratory data and the prediction models for deceased and surviving patients with acute-on chronic liver failure (ACLF)

		Deceased		Surviving		
		Average	SD	Average	SD	
J-HEPM		52.4 ±	19.1	23.5 ±	18.7	p<0.001
MELD-Na score		26.9 ±	4.3	27.5 ±	6.4	n.s.
MELD score		24.4 ±	3.4	26.1 ±	6.8	n.s.
Alb	mg/dL	2.9 ±	1.1	3.0 ±	0.6	n.s.
Cre	mg/dL	0.71 ±	0.32	1.47 ±	1.18	p<0.05
Tbil	mg/dL	12.7 ±	5.5	9.7 ±	5.6	n.s.
AST	IU/L	487 ±	528	1556 ±	1677	p<0.05
ALT	IU/L	446 ±	552	1149 ±	1001	n.s.
AFP	ng/mL	122.7 ±	272.2	61.4 ±	177.1	n.s.
HGF	ng/mL	1.9 ±	1.6	2.1 ±	1.6	n.s.
Plt	10^4/mL	10.8 ±	4.7	16.8 ±	14.2	n.s.
APTT	sec.	45.3 ±	12.8	47.4 ±	18.5	n.s.
PT	%	34.9 ±	13.4	39.3 ±	15.3	n.s.
PTINR		2.10 ±	0.78	2.09 ±	0.69	n.s.

Acute-on chronic liver failure, ACLF; alpha fetoprotein, AFP; albumin, Alb; alanine aminotransferase, ALT; aspartate aminotransferase, AST; APTT, activated partial thromboplastin time; creatinine, Cre; hepatocyte growth factor, HGF; Japan HE prediction model ,J-HEPM; model for end-stage liver disease, MELD; MELD-Na, MELD modified by sodium concentration; platelet, Plt; prothrombin time, PT; PT-INR, PT-international normalized ratio; standard deviation, SD; total bilirubin, Tbil

Table 4. Laboratory data and the prediction models for each etiology of acute-on chronic liver failure (ACLF)

		AIH			Alcohol			HBV				
		Average		SD	Average		SD	Average		SD		
J-HEPM		58.0	±	14.8	29.0	±	21.8	39.9	±	24.4	p<0.05	*
MELD-Na score		23.9	±	2.7	29.7	±	5.6	23.2	±	2.5	p<0.05	**
MELD score		23.1	±	2.1	27.5	±	6.0	21.4	±	2.9	p<0.05	***
Alb	mg/dL	2.7	±	0.6	2.7	±	0.7	3.1	±	0.4	n.s.	
Cre	mg/dL	0.63	±	0.26	1.51	±	1.12	0.59	±	0.12	p<0.05	**
Tbil	mg/dL	14.2	±	5.0	9.8	±	4.8	14.2	±	6.4	n.s.	
AST	IU/L	916	±	495	1310	±	1753	659	±	443	n.s.	
ALT	IU/L	605	±	510	949	±	1097	748	±	467	n.s.	
AFP	ng/mL	38.2	±	48.2	7.9	±	10.5	312.7	±	378.1	n.s.	
HGF	ng/mL	1.6	±	0.8	2.4	±	1.9	1.3	±	0.7	n.s.	
Plt	10^4/mL	12.2	±	2.6	15.4	±	14.6	12.2	±	4.2	n.s.	
APTT	sec.	39.3	±	8.8	49.5	±	18.1	42.3	±	9.9	n.s.	
PT	%	45.5	±	18.0	32.6	±	13.8	44.0	±	7.1	n.s.	
PTINR		1.69	±	0.34	2.39	±	0.79	1.64	±	0.19	p<0.05	**

Acute-on chronic liver failure, ACLF; alpha fetoprotein, AFP; autoimmune hepatitis, AIH; albumin, Alb; alanine aminotransferase, ALT; aspartate aminotransferase, AST; APTT, activated partial thromboplastin time; creatinine, Cre; hepatitis B virus infection, HBV; hepatocyte growth factor, HGF; Japan HE prediction model ,J-HEPM; model for end-stage liver disease, MELD; MELD-Na, MELD modified by sodium concentration; platelet, Plt; prothrombin time, PT; PT-INR, PT-international normalized ratio; standard deviation, SD; total bilirubin, Tbil

Single asterisk (*) indicated statistical significance in AIH to Alcohol, double asterisk (**) in Alcohol to both AIH and HBV, and triple asterisk (***) in AIH to HBV, respectively.