

A Prospective Multicenter Study of the Chinese Scoring System for Hepatitis B Liver Failure

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Research Article

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Abstract

Objective: To evaluate the clinical utility of a Chinese scoring system for hepatitis B liver failure in a prospective and multicenter study.

Methods: Clinical data for 1143 patients with hepatitis B liver failure who had been followed up for a minimum of 6 months were collected from seven liver disease centers across China. The disease severity and prognosis for the patients were predicted using the Chinese scoring system and compared to those predicted with the model for end-stage liver disease (MELD) score, MELD-Na score, and Child-Turcotte Pugh (CTP) score.

Results: The Chinese scoring system was more effective at predicting the outcomes of survival and mortality than the MELD score. In the peak disease stage, the area under the Receiver Operating Characteristic curve for the Chinese scoring system was 0.954, significantly higher than that (0.896) for the MELD scoring system ($P < 0.001$). The positive prediction at 30, 90, and 180 days with the Chinese scoring system was 0.764 (95% confidence interval [CI]: 0.714-0.808), 0.731 (95% CI: 0.694-0.769), and 0.724 (95% CI: 0.679-0.765), also significantly higher than that with the MELD, MELD-Na, and CTP scores ($P < 0.001$). In addition, the Chinese scoring system was superior to the MELD, MELD-Na, and CTP scores ($P < 0.001$) at predicting the prognosis of patients with hepatitis B liver failure at both 30 and 180 days.

Conclusion: The Chinese scoring system demonstrated superior performance to the three established scoring systems in assessing the severity and outcomes of hepatitis B liver failure in this cohort.

Introduction

Liver failure is a severe complication in which the liver fails to perform basic functions due to severe or massive liver injury, which also disrupts the vital functions of other organs and systems. It typically manifests as jaundice, hepatic encephalopathy, and coagulopathy^[1-2]. The mortality rate of liver failure may be as high as 70%^[3]. It is critical that hepatologists are able to assess and predict the outcomes of liver failure accurately and early in patients, especially to determine if and when a liver transplantation is required. Dynamic changes in the conditions of a patient should also be closely monitored and followed, as a timely prevention and treatment of complications significantly impacts the clinical outcomes. The model for end-stage liver disease (MELD), MELD-Na, and Child-Turcotte Pugh (CTP) scores are three established systems used to numerally grade the severity of liver failure in patients, which can reveal the probability for favorable or non-favorable outcomes^[4,5]. All three model systems were established by assessing patients with liver failure mainly caused by hepatitis C virus (HCV) infection and alcoholic liver disease. However, liver failure caused by hepatitis B virus (HBV) infection is characterized by acute onset, severe liver injury, and high mortality, with distinct pathogenesis and clinical characteristics from those caused by HCV and alcohol. The three model systems can be expanded or modified to better grade HBV liver failure. We previously established a new scoring system known as the Chinese scoring system and its performance and utility were evaluated for patients with hepatitis B liver failure in a retrospective study^[6-9]. To further investigate the utility of this new scoring system in grading the severity of hepatitis B liver failure and predicting outcomes, we conducted this prospective study at seven liver disease centers across China.

Ethics Statement

All procedures performed in studies involving human participants were approved by Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

Materials And Methods

1. Patients

1.1 Enrollment Between October 2013 and June 2016, a total of 1143 chronic hepatitis B inpatients with liver failure (acute-on-chronic liver failure, ACLF) were enrolled from seven liver disease centers across China (infection department of the Third Affiliated Hospital of Sun Yat sen University, infection department of the First Affiliated Hospital of Zhejiang University, Shanghai Ruijin Hospital, Xiangya Hospital of Central South University, Qilu Hospital of Shandong University, Shandong Provincial Hospital, and Xuzhou Medical College). Among them, 936 were men, 207 were women, and the average age was 43.4 ± 12.6 (ranged from 18 to 65). The patients were followed up for >6 months, during which 464 died and 680 survived.

HBV-related ACLF diagnosis for all patients followed the criteria established by the 18th Asia-Pacific Association of Liver Research consensus on chronic-acute liver failure^[10]. The criteria include a history of chronic hepatitis B and acute flare-up of liver injury with clinical manifestations of jaundice (total bilirubin ≥ 85 $\mu\text{mol/L}$) and coagulation disorder (prothrombin time international standardized ratio ≥ 1.5), ascites and / or hepatic encephalopathy within 4 weeks.

1.2 Inclusion criteria Male or female patients aged 18-60; HBsAg-positive history > 6 months, HBV DNA-positive, HBeAg-positive or negative; persistent hepatitis symptoms of fatigue, anorexia, abdominal distention, or yellow urine; gradual aggravation of jaundice over a short period of time; total serum bilirubin ≥ 85 $\mu\text{mol/L}$ or daily elevation ≥ 17.1 $\mu\text{mol/L}$; abnormal coagulation function, and international standardized ratio of prothrombin time ≥ 1.5 .

1.3 Exclusion criteria Patients were excluded if they: (1) had other hepatitis virus infection; (2) had human immunodeficiency virus infection, biliary, alcoholic liver, or autoimmune liver diseases; drug poisoning, liver tumors, or were undergoing liver transplantation, renal insufficiency, or long-term anticoagulant therapy related to renal diseases.

2. Observations and follow-up endpoints Clinical information and test findings for all patients at and after admission were collected weekly. The clinical information mainly consisted of the stages of hepatic encephalopathy. Laboratory findings included serum total bilirubin, albumin, creatinine, prothrombin time, prothrombin time international normalized ratio (INR), serum sodium ion concentration, liver size (B-mode ultrasound measurement), ascites, and pleural effusion (B-ultrasound measurement), as well as infection (peripheral white blood cell count, neutrophil ratio, and chest inflammation images). The end point of 180 days of follow-up was used to determine the survival rate. The death count included patients that rejected rescue treatment and were discharged from the hospital as well as patients that died during the hospital stay or within 180 days of follow-up.

3. Score calculation

3.1 MELD score Since all subjects had hepatitis B-related liver failure, the MELD score was calculated as $3.8 \times \log_e(\text{serum bilirubin } \mu\text{mol/L} \times 0.058) + 1.2 \times \log_e(\text{prothrombin time INR}) + 9.6 \times \log_e(\text{serum creatinine } \mu\text{mol/L} \times 0.011) + 6.4$ ^[6].

3.2 MELD-Na This score was calculated as $\text{MELD} + 1.59 \times (135 - \text{Na}^+)$, wherein serum Na^+ levels ≥ 135 mmol/L were treated as 135 mmol/L, ≤ 120 mmol/L as 120 mmol/L, and between 120~135 mmol/L as the specific value^[7].

3.3 CTP score This score was calculated using the scoring standards for five indexes, i.e. grade of hepatic encephalopathy, ascites, total bilirubin, albumin, and prolonged prothrombin time. A score of 1, 2, or 3 was assigned to each index to reflect the severity of each condition, and the CTP score was the sum of the five indexes^[8].

3.4 Chinese scoring system This system consists of seven clinical indicators: prothrombin activity, serum creatinine, hepatic encephalopathy, serum total bilirubin, liver size (B-ultrasonic measurement), ascites/pleural fluid (B-ultrasonic measurement) volume, and infection (peripheral blood leukocyte count, neutrophil ratio, and chest inflammation image). A score of 1, 2, 3, or 4 was assigned to each indicator to reflect the severity, and the sum of the seven indicator scores was used (see Table 1 for details).

4. Statistical analysis

(1) All numeral data were expressed as mean \pm standard deviation (\pm s) and the difference was computed using the f test. (2) The count data were expressed as percentage (%), and the difference was assessed with the χ^2 test. (3) Assessments of the short-term and long-term prognoses for patients with hepatitis B liver failure using the Chinese scoring system, MELD score, MELD-Na score, and CTP score were compared using receiver operating characteristic (ROC) curves and the ROC area under the curve (AUC). AUC $>$ 0.7 was deemed to be of clinical utility and $>$ 0.8 to be of good prediction accuracy. The AUC values were compared using normal Z tests and the ROC curve sensitivity and specificity were used to determine the best cut-off values for the score and the Youden index. SPSS 18.0 statistical software was used for all analyses. $P <$ 0.05 was considered statistically significant.

Results

1. Demographic features and groups. A total of 1143 patients with hepatitis B liver failure were enrolled in this study. Among them, 936 were men and 207 were women, and the mean age was 43.4 ± 12.6 years old (ranged between 18 and 65). A total of 463 patients died while the remaining 680 survived (Table 2).

2. The cutoff value and distribution range for the Chinese scoring system and the MELD score to separate the patients that survived from those that did not. The cutoff value of 12.14 with the Chinese scoring system separated 83.65% of patients in the survival and death groups, i.e. 83.65% patients in the survival group scored between 3.68 and 12.14 points, while 83.65% patients in the death group scored between 12.14 and 22.13 points. With the MELD score, the cutoff value was 31.78; 64.52% of patients in the survival group scored between 20.37 and 31.78 points, and 64.52% of patients in the death group scored between 31.78 and 49.88 points (see Figure 1 and Figure 2, $P <$ 0.01).

3. Comparison of the performance to grade the severity at the peak disease with the Chinese scoring system and MELD scoring system The ROC curve was plotted using the total scores. The area under the ROC curve for the Chinese scoring system was 0.954 (95% confidence interval [CI]: 0.943-0.971) and the standard error was 0.013, with $P <$ 0.001, suggesting good prediction performance. The area under the ROC curve for the MELD score was 0.896 (95% CI: 0.881-0.924), indicating less effectiveness than the Chinese score system (see Figure 3 and table 3).

4. The ability to predict and differentiate disease outcomes at different times with different scoring systems The predictive values for the outcomes on days 30, 90, and 180 after discharge using the Chinese scoring system were 0.764 (95% CI: 0.714-0.808), 0.731 (95% CI: 0.694-0.769), and 0.724 (95% CI: 0.679-0.765), respectively, which were significantly higher than those for the other three scoring systems (see Table 4, $P <$ 0.001).

5. Comparison of the performance predicting short-term (30 days) prognosis for patients with hepatitis B liver failure using the Chinese scoring system, MELD score, MELD Na score, and CTP score The area under the ROC curve with the total score from the Chinese scoring system was 0.783 (95% CI: 0.732-0.865) and the standard error was 0.026, with $P <$ 0.001, suggesting good predictive performance. The areas under the ROC curves for the MELD score, MELD Na score, and CTP score were 0.706 (95% CI: 0.623-0.778), 0.716 (95% CI: 0.644-0.779) and 0.686 (95% CI: 0.623-0.767), respectively, which were significantly lower than that for the Chinese scoring system (see Figure 4 and table 5).

6. Comparison of the performance predicting long-term (180 days) prognosis for patients with hepatitis B liver failure using Chinese scoring system, MELD score, MELD-Na score, and CTP score The area under the ROC curve with the total score from the Chinese scoring system was 0.748 (95% CI: 0.692-0.837) and the standard error was 0.022, with $P <$ 0.001, suggesting good predictive performance. The areas under the ROC curves for the MELD score, MELD Na score, and CTP score were 0.657 (95% CI: 0.588-0.725), 0.676 (95% CI: 0.605-0.743), 0.682 (95% CI: 0.621-0.752), respectively, which were significantly lower than that for the Chinese scoring system (see Figure 5 and table 6).

Discussion

MELD, MELD-Na, and CTP scores have been established to address the need to accurately identify patients with liver failure who require liver transplants. All three systems are widely accepted in the clinical setting. However, these models were constructed using clinical data largely from patients with liver failure in Europe and the United States where the major etiologies for liver failure are alcohol, drugs, hepatitis C, and cholestasis. In contrast, hepatitis B represents the dominant etiology for liver failure in China and is responsible for 85% of liver failure cases in the country^[11]. Therefore, these three models^[12-13] may not completely fit Chinese patients with liver failure. As noted by Lin Xianfeng et al^[14], the MELD score failed to accurately predict the prognosis of 327 Chinese patients with hepatitis B liver failure. One factor that may have affected this result is that patients with HBV liver failure do not respond well to comprehensive treatment and often need an artificial liver, liver transplant, or other treatment urgently. The other factor is that chronic HBV infection may exhaust patients' immunity, leading to severe complications. A new system that takes these factors into consideration is required^[15].

CTP has been widely employed in managing patients with liver diseases because of its simplicity and ease of calculation. However, it is often hindered by a lack of consistency as CTP is mainly based on albumin level and prothrombin time, both of which can be masked if exogenous albumin and plasma products are infused. In addition, hepatic encephalopathy and ascites measurement can be subjective and variable. CTP only consists of three grades with a narrow score range of 5-15, which limits the ability to differentiate. Patients with the same score may differ greatly in the severity of liver disease.

Although the MELD and MELD-Na scoring systems are recognized as easy to use, reproducible, and accurate in clinical applications, they bear an inherent limitation because they only include bilirubin, coagulation function, renal function, and etiology, while excluding the complications of liver failure (infection, hemorrhage, hepatic encephalopathy, brain edema, or ascites). The Na concentration in the MELD-Na scoring system can be easily affected by insufficient intake, diuretics, or sodium pump failure^[16-21]. A study conducted in China^[22] showed that the AUC of MELD and MELD-Na scores for the 12-week outcomes of patients with hepatitis B-related liver failure was only 0.731, 0.735, and 0.773, respectively, and the sensitivity was below 0.7.

This prospective study conducted at seven large liver disease centers across China showed that the Chinese scoring system better distinguished patients that survived from those who did not, in comparison to MELD ($P < 0.001$). The area under the ROC curve for the Chinese scoring system was 0.954 in the peak disease stage, suggesting a stronger ability to grade the severity of liver failure. The AUC for the MELD scoring system was 0.896, which was relatively high, but significantly lower than that for the new scoring system ($P < 0.001$). We also found that the efficiency in predicting outcomes on the 30th, 90th, and 180th day after discharge with the Chinese scoring system was significantly higher than that with MELD, MELD Na, and CTP ($P < 0.001$).

Massive or submassive liver injury following a flare-up of HBV replication or HBV reactivation compromises synthetic, metabolic, and detoxification functions in the liver, leading to reduced albumin levels and ascites, hyperbilirubinemia, decreased PTA(Prothrombin activity), increased international standard ratio of prothrombin (INR), and hepatic encephalopathy. In addition, a severely injured liver may also hurt Kupffer cell function and reduce complement levels that may limit the anti-infective capacity. The accumulation of toxins and a decrease in renal blood flow may facilitate hyperbilirubinemia, renal function insufficiency, or even renal failure. In theory, the severity of liver failure among different individuals can be indicated by biomarkers that reflect critical alterations in the pathophysiology of liver failure. Thus, we formulated this new scoring system to improve severity grading and outcome prediction. A total of seven clinical indicators of hepatitis B liver failure are included in the Chinese scoring system, consisting of not only objective indicators such as Cr, total bilirubin, PTA, and liver size, but also the complications of hepatic encephalopathy, ascites with pleural effusion, and pulmonary infection, which reflect the pathophysiological changes resulting from hepatitis B liver failure. The score boundary point was confirmed using the interactive chi square test, guided by the principle that emphasizes simplicity and clarity. Each index is graded between 0-4 points, allowing a high degree of differentiation that increases prediction accuracy.

This new scoring system utilizes common clinical indicators, which can be routinely ordered to allow easy and wide applications.

This new scoring system demonstrated superior performance in grading the severity and predicting the outcomes of HBV liver failure in this cohort compared to the three established scoring systems, representing progress in improving the management of HBV liver failure. However, our findings will need further verification in larger cohorts that include not only patients with HBV liver failure, but also those with liver failure with other etiologies.

Declarations

Conflict of interest: No any editorial or financial conflict of interest exists.

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Author contributions: Wu Zhebin performed case summary and statistical analysis, and wrote the manuscript; Ke Weimin designed this scoring system; Lin Bing-liang and Peng Liang were responsible for statistical analysis; Chen Zhi, Zhang Xin-xin, Tan De-ming, Ren Wan-hua, Wang Kai and Yan Xue-bin were responsible for case enrollment and data collection in other subcenters; Zhiliang Gao was responsible for research design and the whole quality of the study.

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Tables

Table 1
Assigned scores of the Chinese scoring system

Scoring (score)	Hepatic encephalopathy (Stage)	Total bilirubin (μmol/L)	The maximum depth of ascites(mm)	Activity of PT(%)	Right hepatic oblique diameter/thickness (mm)	Creatinine (μmol/L)	Infection (depend on WBC 10 ⁹ /L)
1	0	≥ 10 ~ 20ULN	> 0 ~ 40	30 ~ < 40	Oblique diameter ≥ 120 or Thickness ≥ 110	> 1.0 ~ 1.1ULN	WBC > 10 ~ 15 Or N > 70%~80%
2	0	> 20 ~ 30ULN	> 40 ~ 80	20 ~ < 30	Oblique diameter 110 ~ < 120 or Thickness 100 ~ < 110	> 1.1 ~ 1.2ULN	WBC > 15 ~ 20 Or N > 80%~90%
3	0	> 30 ~ 40ULN	> 80	10 ~ < 20	Oblique diameter 100 ~ < 110 or Thickness 90 ~ < 100	> 1.2 ~ 1.3ULN	WBC > 20 Or N > 90%
4	0	> 40ULN	> 80 + one or both side pleural fluid	< 10	Oblique diameter < 100 or Thickness < 90	> 1.3ULN	Inflammation manifestation of lung

ULN: Upper limit of normal.

Score of ascites: Regardless of the amount of ascites, the presence of unilateral or bilateral pleural fluid is counted as 4 points.

Liver size scoring: If the right liver oblique diameter and thickness are measured at the same time on the ultrasound image, the high-scoring scoring results are taken.

Infection score: The standard of 4 points is the imaging changes of pulmonary inflammation, regardless of the white blood cells And neutrophil counted as 4 points.

Table 2
Baseline characteristics of included patients at admission

Parameters	Death group (n = 463)	Survival group (n = 680)	t/x2 value	P
Age (year)	45.38 ± 11.73	40.06 ± 10.47	1.84	0.12
Males (%)	364/99	572/108	1.99	0.06
WBC (×10 ⁹ /L)	7.82 ± 3.54	6.98 ± 3.72	1.25	0.38
ALT (U/L)	568.47 ± 376.94	629.76 ± 504.57	1.56	0.28
Albumin (g/L)	31.64 ± 3.56	32.85 ± 4.02	0.98	0.47
TB (Imol/L)	428.75 ± 284.63	353.96 ± 249.66	3.45	< 0.001
PTA (%)	29.86 ± 11.58	34.38 ± 10.85	4.78	< 0.001
INR	3.41 ± 0.68	2.83 ± 0.62	4.27	< 0.001
BUN/(mmol/L)	5.84 ± 3.68	5.22 ± 3.76	1.96	0.08
CR/(μmol/L)	82.37 ± 54.16	67.47 ± 44.85	1.92	0.09
HBV DNA,median(range), Log ₁₀ IU/ml	6.89 (4.30–8.86)	6.62(5.02–8.64)	1.89	0.16
Without cirrhosis, n(%)	296(63.93)	258(37.94)	8.94	< 0.001
Encephalopathy (%)	16.58	9.73	10.76	< 0.001
HRS (%)	8.23	5.13	2.95	< 0.001
SBP (%)	54.32	31.06	6.83	< 0.001
Ascites (%)	67.43	48.14	3.12	< 0.001
MELD	40.52 ± 6.83	26.84 ± 6.18	16.83	< 0.001
MELD-Na	44.76 ± 7.83	28.62 ± 5.93	19.05	< 0.001
CTP	11.87 ± 1.68	10.56 ± 1.47	2.01	0.04
Chinise scoring system	17.53 ± 3.92	8.46 ± 3.28	22.18	< 0.001

Table 3
Comparison of the performance to grade the severity at the peak disease by Chinese scoring system and MELD scoring system

	AUROC(95% CI)	p value vs. CSS-LFB
CSS-LFB	0.954 (0.943–0.971)	
MELDs	0.896(0.881–0.924)	< 0.001

Table 4

The ability to predict and differentiate disease outcomes at different times with different scoring systems

	CSS-LFB C-index (95% CI)	MELD C-index (95% CI)	MELD-Na C-index (95% CI)	Child-Pugh C-index (95% CI)
30-day mortality p value vs.CSS	0.764 (0.714–0.808)	0.684 (0.632–0.743) < 0.001	0.685 (0.634–0.738) < 0.001	0.664 (0.612–0.725) < 0.001
90-day mortality p value vs.CSS	0.731 (0.694–0.769)	0.657 (0.612–0.713) < 0.001	0.662 (0.616–0.712) < 0.001	0.656(0.607–0.704) < 0.001
180-day mortality p value vs.CSS	0.724 (0.679–0.765)	0.648 (0.604–0.698) < 0.001	0.655 (0.607–0.699) < 0.001	0.642 (0.593–0.691) < 0.001

Table 5

Comparison of the area under the ROC curve of predicting short-term (30 days) prognosis of patients with hepatitis B liver failure among Chinese scoring system, MELD score, MELD Na scoring and CTP scoring

	AUROC (95% CI)	p value vs. CSS-LFB
CSS-LFB	0.783 (0.732–0.865)	
MELDs	0.706 (0.623–0.778)	0.0089
MELD-Nas	0.716 (0.644–0.779)	0.0097
CPs	0.686 (0.623–0.767)	0.0075

Table 6

Comparison of the area under the ROC curve of predicting long-term (180 days) prognosis of patients with hepatitis B liver failure among Chinese scoring system, MELD score, MELD-Na scoring and CTP scoring

	AUROC (95% CI)	p value vs. CSS-LFB
CSS-LFB	0.748(0.692–0.837)	
MELDs	0.657 (0.588–0.725)	0.0014
MELD-Nas	0.676 (0.605–0.743)	0.0082
CPs	0.682 (0.621–0.752)	0.0012

Figures

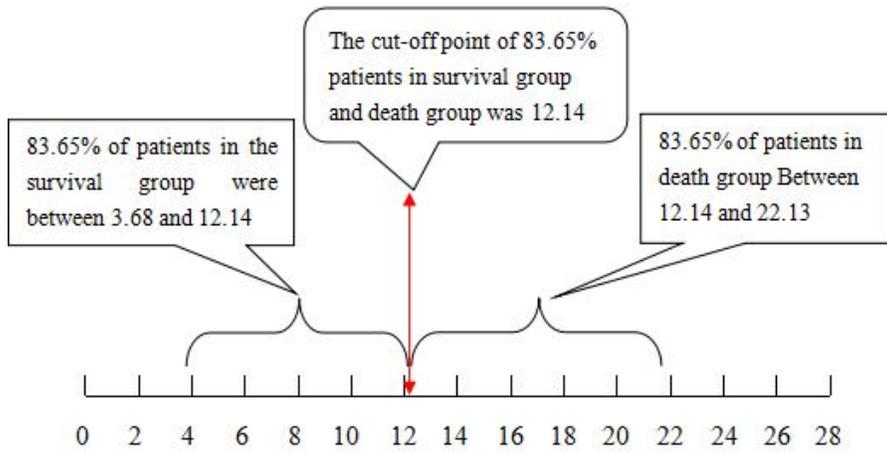


Figure 1

The cutoff value and distribution range for the Chinese scoring system to separate the patients that survived from those that did not.

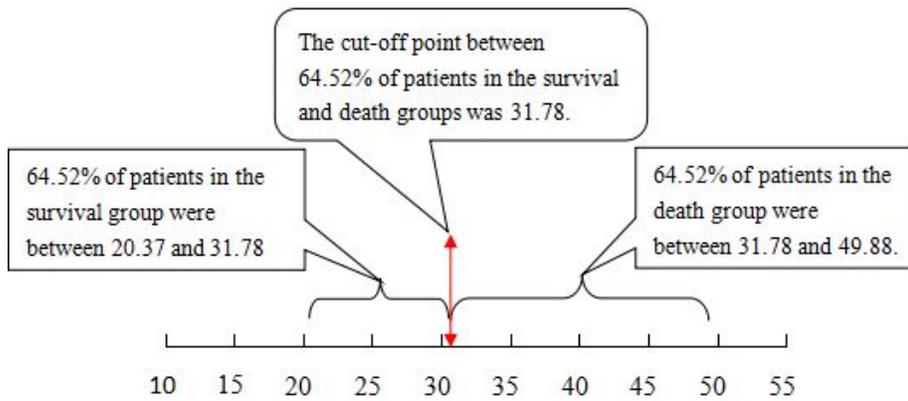


Figure 2

The cutoff value and distribution range for the MELD score to separate the patients that survived from those that did not.

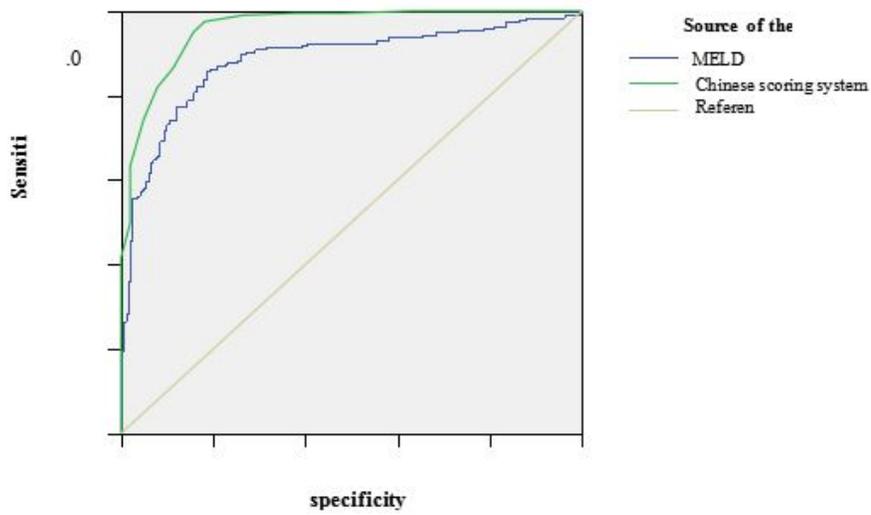


Figure 3

The ROC curve of Chinese scoring system and MELD scoring system at the peak disease.

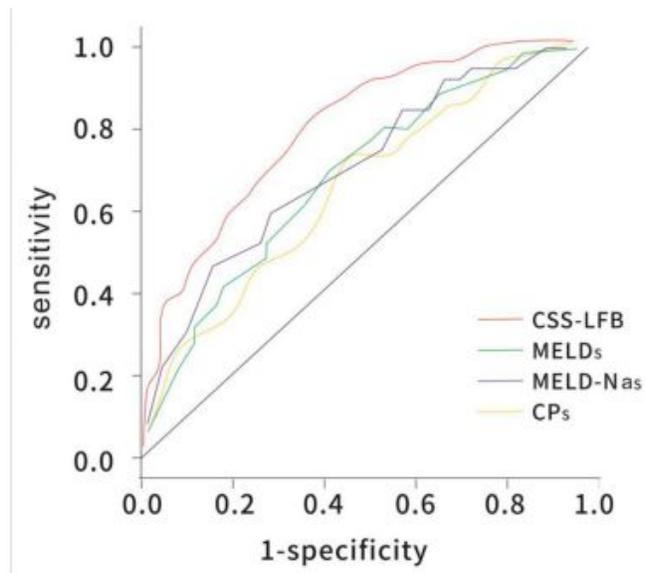


Figure 4

The ROC curve of predicting short-term (30 days) prognosis of patients with hepatitis B liver failure among Chinese scoring system, MELD score, MELD Na scoring and CTP scoring.

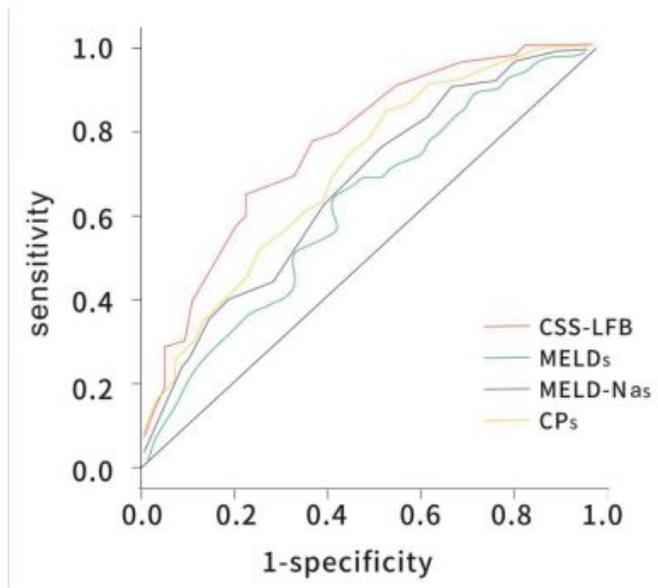


Figure 5

the ROC curve of predicting long-term (180 days) prognosis of patients with hepatitis B liver failure among Chinese scoring system, MELD score, MELD Na scoring and CTP scoring.