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Research Article

Lactate and Bilirubin Index: A New Indicator to Predict Critically Ill Cirrhotic Patients' Prognosis

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Objectives. We aimed to perform external validation of the prognostic value of the lactate and bilirubin (LB) index, a new indicator, and compare the ability of the LB index and other scoring systems to predict both short- and long-term mortality in critically ill cirrhotic patients. *Materials and Methods*. A number of 479 cirrhotic patients admitted into ICU were included in our research. We measured prognostic scores in the first 24 hours including LB index, Child–Pugh, SOFA, CLIF-SOFA, and MELD scores. The LB index was calculated as follows: ln [1000 × lactate (mmol/L) × bilirubin (μmol/L)]/2. The primary outcomes were 28-day and 3-year all-cause mortality. Multivariate logistic regression analyses were used to investigate the independent association between the LB index and the mortality in critically ill cirrhotic patients. The area under the receiver operating characteristic curve was used to assess the prediction accuracy of short- and long-term mortality of the clinical score. Calibration of the score was evaluated by Hosmer–Lemeshow goodness-of-fit test for significance. *Results*. Multivariate logistic regression analysis identified that the LB index (odds ratio: 5.487, 95% confidence interval: 3.542–8.501, $P < 0.001$) was the strongest predictor for 28-day mortality. The LB index gave the highest area under the curve (0.791, 95% confidence interval: 0.747–0.836) in predicting 28-day mortality. For predicting 3-year mortality, the model for end-stage liver disease (MELD) score showed better discrimination ability with an area under the curve of 0.726 (95% confidence interval: 0.680–0.771). The risk of mortality significantly increased when the clinical scores were ≥ the optimal cutoff values. *Conclusions*. The LB index, a simple prognostic indicator, performs well in predicting critically ill cirrhotic patients' short-term prognosis, while, for long-term prognosis, the MELD score is more appropriate.

1. Introduction

Cirrhotic patients often require entering an intensive care unit (ICU) due to life-threatening complications [1–3]. Decompensated cirrhotic patients are often accompanied by progressive organ failure [4, 5]. According to statistics, hospital mortality of cirrhotic patients in ICU ranges from 34 to 86% [4]. Various clinical models have been developed to evaluate the severity of cirrhosis accurately so as to determine the optimum therapeutic regimen, including Child–Pugh system [6], sequential organ failure assessment(SOFA) [7], chronic liver failure-sequential organ failure assessment (CLIF-SOFA) [8], and model for end-stage liver disease (MELD) score [9]. They were externally validated in cirrhotic patients entering ICU [10–12].

Lactate production increases and utilization decreases on account of tissue hypoxia and impaired mitochondrial oxidation [13]. Yet, up to seventy percent of whole-body lactate is cleared in the liver [14, 15]. Increased lactate levels are not only associated with acute hepatic impairment, but also independently associated with critically ill cirrhotic patients' mortality [16–20]. Besides, total bilirubin is an important index of liver function. Therefore, we proposed the lactate and bilirubin (LB) index, a new indicator to predict critically ill cirrhotic patients' prognosis, which was convenient and practical compared to other scoring systems. In addition, we discovered that little was known about the value of the LB index and the scoring systems mentioned above in predicting critically ill cirrhotic patients' short- and long-term prognosis. Thus, our research's objective was to perform

external validation of the prognostic value of the LB index and compare the ability of the LB index and the scoring systems mentioned above to predict both short- and long-term mortality in critically ill cirrhotic patients.

2. Materials and Methods

2.1. Data Source. The Medical Information Mart for Intensive Care III is an open-access database, including information about patients who entered ICU between 2001 and 2012 [21]. After finalization of the National Institute of Health' *s* training course named "Protecting Human Research Participants," we granted access to the database (certificate number: 36072928). The institutional review boards of the Massachusetts Institute of Technology had approved the establishment. Ethics committee approval was not necessary for this manuscript. The research was a retrospective observational research, all information relating to patients in the database anonymous; therefore, informed consent was not necessary.

2.2. Study Population. Patients who were at least 18 years old at their first ICU admission and stayed more than 24 h were selected. The diagnosis of liver cirrhosis was based on the following features: (a) characteristic clinical evidence such as jaundice, (b) abnormal laboratory findings such as thrombocytopenia, (c) imaging findings such as signs of portal hypertension, and (d) histopathology [22, 23]. Exclusion criteria were as follows: (a) acquired immune deficiency syndrome, (b) carcinoma, (c) liver transplantation, and (d) total bilirubin or lactate data lost at ICU admission. After applying exclusion criteria, the study sample group included 479 patients with cirrhosis.

2.3. Data Collection. Clinical parameters we collected from the database included demographic data, vital signs, and laboratory parameters. Laboratory parameters included white blood cell count, hemoglobin, platelet count, prothrombin time, glucose, blood urea nitrogen, creatinine, albumin, total bilirubin, and arterial blood lactate. The average values of each parameter within the first 24 h after being admitted to ICU were used to calculate the scores of clinical models. Child–Pugh, SOFA, CLIF-SOFA, and MELD scores were calculated using the formulae published [6–9]. The LB index was calculated as follows: $\ln[1000 \times \text{lactate (mmol/L)} \times \text{bilirubin } (\mu\text{mol/L})]/2$. The start date for follow-up was the date of admission. All participants were followed up for at least 3 years. The outcomes of our research were 28-day, 90-day, 1-year, and 3-year all-cause mortality. The primary endpoints were 28-day and 3-year all-cause mortality.

2.4. Statistical Analysis. All statistical procedures were performed with STATA (version 14.0; StataCorp, State of Texas, USA). Quantitative variables were compared by Mann–Whitney *U* test, presented as median [interquartile range (IQR)]. Categorical variables were expressed absolute numbers (frequencies) and compared by Chi-square test or Fisher's exact test. Multivariate logistic regression analyses were used to investigate the independent association between various clinical parameters and mortality in critically ill cirrhotic patients, while controlling for potential confounding. Odds ratio (OR) was reported with 95% confidence interval (CI). Receiver operating characteristic curves were generated to evaluate the accuracy of clinical models in predicting mortality. Calibration of the score was evaluated by Hosmer–Lemeshow goodness of fit test for significance ($P > 0.05$). The comparison between the area under the curve (AUC) was performed using DeLong test [24]. The sensitivity and specificity at an optimal cutoff value were compared among different clinical models. All the participants were divided into two groups (relatively low risk and high risk) by the optimal cutoff value of clinical scores according to the curve. All the tests were two-sided. A P value less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics of the Study Population. A number of 479 participants were included in our research. The baseline characteristics of the participants in both survivor cohort and nonsurvivor cohort are listed in Tables 1 and 2 in detail. All the patients' median age was 55.6 years; 315 were male and 164 were female. The majority of participants were white. The predominant cause of cirrhosis was alcohol. A total of 60 patients had two causes of cirrhosis and three patients had three. Infection and sepsis were the most common causes of ICU hospitalization. The survivor and nonsurvivor cohorts were similar in age, sex, weight, comorbidity, length of ICU stay, hemoglobin, glucose, and albumin ($P \geq 0.05$). Nonsurvivors scored higher than survivors in these clinical scores including LB index, MELD, Child–Pugh, SOFA, and CLIF-SOFA scores (all $P < 0.001$).

3.2. Results of Multivariate Logistic Regression Analysis. The results of parameters significant in the multivariate logistic regression are shown in Table 3. As the results show, the LB index was the strongest predictor for 28-day mortality. Furthermore, age, length of ICU stay, mechanical ventilation duration, BUN, PTT, and respiratory rate were also identified as independent risk factors for 28-day mortality in cirrhotic patients entering ICU.

3.3. Comparison of Different Scoring Systems in Predicting 28-Day and 3-Year Mortality in Critically Ill Cirrhotic Patients. Figure 1 shows that the LB index performed the best in predicting 28-day mortality. Figure 2 shows that the performance of LB index, Child–Pugh, SOFA, and CLIF-SOFA scores was worse while the MELD score still performed well in predicting 3-year mortality. More details about the performance of different scoring systems are presented in Tables 4 and 5. The calibration curve of the LB index for 28-day mortality is shown in Figure 3 ($P = 0.728$).

Table 1: Characteristics of the study population, stratified by survival.

Parameter	All patients ($n = 479$)	Survivors ($n = 321$)	Nonsurvivors ($n = 158$)	P value
Age (years)	55.6 (48.9–64.8)	55.8 (48.3–65.2)	55.2 (49.9–64.3)	0.710
Sex: male	315 (65.8)	213 (66.4)	102 (64.6)	0.697
Weight (kg)	85.3 (70.9–99.0)	85.3 (70.5–97.5)	85.0 (71.2–100.0)	0.660
Ethnicity				
White	350 (73.1)	241 (75.1)	109 (69.0)	0.041
Black	31 (6.5)	24 (7.5)	7 (4.4)	
Others	98 (20.5)	56 (17.4)	42 (26.6)	
Causes of cirrhosis				
Alcoholic	264 (55.1)	167 (52.0)	97 (61.4)	0.053
Hepatitis B	12 (2.5)	5 (1.6)	7 (4.4)	0.059
Hepatitis C	119 (24.8)	77 (24.0)	42 (26.6)	0.537
Biliary	9 (1.9)	0 (0.0)	9 (5.7)	0.034
Autoimmune	5 (1.0)	3 (0.9)	2 (1.3)	0.667
Others	136 (28.4)	103 (32.1)	33 (20.9)	0.011
Primary cause of ICU admission				
Infection/sepsis	132 (27.6)	93 (29.0)	39 (24.7)	0.323
Bleeding	107 (22.3)	79 (24.6)	28 (17.7)	0.089
Respiratory	17 (3.5)	12 (3.7)	5 (3.2)	0.750
Cardiovascular	56 (11.7)	42 (13.1)	14 (8.9)	0.176
Renal failure	25 (5.2)	12 (3.7)	13 (8.2)	0.038
Neurological failure	49 (10.2)	31 (9.7)	18 (11.4)	0.556
Others	93 (19.4)	52 (16.2)	41 (25.9)	0.011
Comorbidity				
Hypertension	122 (25.5)	80 (24.9)	42 (26.6)	0.695
Diabetes	124 (25.9)	85 (26.5)	39 (24.7)	0.673
Vital signs				
Temperature (°C)	36.7 (36.3–37.2)	36.8 (36.4–37.3)	36.4 (36.0–37.0)	<0.001
Heart rate	90.4 (78.7–103.2)	88.6 (76.8–101.1)	94.2 (81.1–105.4)	0.021
MAP (mmHg)	73.1 (67.9–80.7)	74.8 (69.4–82.5)	70.0 (64.4–75.6)	<0.001
Respiratory rate	18.9 (16.1–22.1)	18.3 (15.9–21.0)	20.2 (17.3–23.7)	<0.001
SpO2/FiO2	185.2 (173.1–457.0)	204.6 (175.2–458.1)	175.8 (169.4–455.8)	<0.001
24-h urine output (mL)	1151 (572–1915)	1360 (787–2028)	653 (222–1280)	<0.001
Mechanical ventilation duration (hours)	36.0 (0.0–120.5)	19.0 (0.0–112.5)	60.1 (12.0–146.5)	<0.001
Length of ICU stay (days)	4.0 (2.4–8.5)	3.8 (2.3–8.0)	4.7 (2.8–9.0)	0.147

Values are expressed as n (%) or median (IQR). ICU: intensive care unit; MAP: mean arterial pressure; SpO2: peripheral oxygen saturation; FiO2: fraction of inspired oxygen.

3.4. Groups and Outcomes. The 28-day, 90-day, 1-year, and 3-year death rates of all the participants were 33.0% (158/479), 41.8% (200/479), 48.6% (233/479), and 57.6% (276/479), respectively. On the basis of the LB index classification (low risk: <6.18 and high risk: ≥6.18), the 28-day, 90-day, 1-year, and 3-year death rates for the patients with low risk were 16.0% (48/300), 24.7% (74/300), 33.0% (99/300), and 44.7% (134/300), respectively, and for the patients with high risk, 61.5% (110/179), 70.4% (126/179), 74.9% (134/179), and 79.3% (142/179), respectively (all $P < 0.001$), while, on the basis of the MELD classification (low risk: <18 and high risk: ≥18), the 28-day, 90-day, 1-year, and 3-year death rates were 16.9% (45/266), 23.7% (63/266), 32.0% (85/266), and 42.9% (114/266), respectively, for the patients with low risk, and 53.1% (113/213), 64.3% (137/213), 69.5% (148/213), and 76.1%(162/213), respectively, for the patients with high risk (all $P < 0.001$). The risk of mortality significantly increased when the clinical scores were ≥ the cutoff values.

4. Discussion

In the research, we performed for the first time external validation of the prognostic value of blood LB index and compared for the first time the ability of the LB index, Child–Pugh, MELD, SOFA, and CLIF-SOFA scores to predict both short- and long-term mortality in critically ill cirrhotic patients.

As this study shows, mortality in critically ill patients with cirrhosis was high, which was comparable to the previous reports [4, 5, 25, 26]. We found that cirrhotic patients in ICU had poor outcomes despite aggressive medical interventions. Therefore, in order to determine the best treatment timely and improve long-term quality of life, it is quite necessary to assess the severity of disease and long-term prognosis in critically ill cirrhotic patients.

The Child–Pugh score was originally developed to determine the risk of surgery for portal decompression in cirrhotic patients, which was also used to assess prognosis of

Table 2: Laboratory parameters and clinical scores of the study population, stratified by survival.

Parameter	All patients ($n = 479$)	Survivors ($n = 321$)	Nonsurvivors ($n = 158$)	P value
Laboratory parameters				
Hb (mg/dL)	9.9 (9.0–11.1)	10.0 (9.1–11.2)	9.8 (8.8–11.0)	0.104
WBC (10^9/L)	10.5 (7.4–15.7)	10.2 (7.3–14.4)	11.6 (7.7–19.1)	0.007
Platelet (10^9/L)	101.2 (70.3–152.0)	110.2 (74.3–162.0)	88.5 (62.3–129.0)	<0.001
INR	1.7 (1.5–2.1)	1.6 (1.4–1.9)	2.0 (1.7–2.7)	<0.001
PT (seconds)	18.0 (15.6–21.4)	16.8 (15.3–19.2)	20.6 (17.5–24.6)	<0.001
PTT (seconds)	39.5 (33.6–48.7)	37.4 (32.4–43.5)	45.3 (38.4–62.7)	<0.001
Glucose (mg/dL)	125.6 (103.0–157.8)	125.6 (103–156.5)	124.4 (101.2–158.0)	0.803
Sodium (mEq/L)	138.0 (134.0–141.0)	138.3 (135.6–141.2)	136.0(132.0–141.0)	<0.001
Potassium(mEq/L)	4.1 (3.7–4.5)	4.1 (3.7–4.4)	4.3 (3.8–4.8)	0.001
BUN (mg/dL)	29.5 (17.0–50.0)	25.3 (15.5–42.3)	41.7 (26.5–63.3)	<0.001
Creatinine (mg/dL)	1.3 (0.8–2.5)	1.1 (0.7–1.9)	1.9 (1.2–3.3)	<0.001
Albumin (g/dL)	2.8 (2.6–3.0)	2.8 (2.6–3.0)	2.8 (2.5–3.1)	0.702
Bilirubin (mg/dL)	3.3 (1.6–7.6)	2.7 (1.3–4.6)	7.3 (3.2–16.1)	<0.001
Lactate (mmol/L)	2.2 (1.6–3.7)	2.0 (1.5–3.0)	2.9 (2.0–6.0)	<0.001
Clinical scores				
Child–Pugh	10 (9–11)	10 (9–11)	11 (10–11)	<0.001
SOFA	9 (6–11)	8 (6–10)	11 (9–14)	<0.001
CLIF-SOFA	9 (7–12)	9 (6–10)	12 (10–15)	<0.001
MELD	16 (10–25)	13 (8–20)	24 (16–33)	<0.001
LB index	5.9 (5.4–6.5)	5.7 (5.3–6.1)	6.6 (5.9–7.0)	<0.001

Values are expressed as n (%) or median (IQR). Hb: hemoglobin; WBC: white blood cell; INR: international normalized ratio; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; SOFA: sequential organ failure assessment; CLIF-SOFA: chronic liver failure-sequential organ failure assessment; MELD: model for end-stage liver disease; LB: lactate and bilirubin.

Table 3: Multivariate regression results of 28-day mortality for critically ill patients with cirrhosis.

Parameter	OR	95% CI		P value
		Lower	Upper	
Age (years)	1.034	1.012	1.057	0.002
Length of ICU stay (days)	0.860	0.785	0.942	0.001
Mechanical ventilation duration (hours)	1.006	1.002	1.010	0.005
BUN (mg/dL)	1.015	1.005	1.025	0.002
PTT (seconds)	1.032	1.017	1.048	<0.001
Respiratory rate	1.069	1.015	1.127	0.012
LB index	5.487	3.542	8.501	<0.001

ORs and P values were estimated using multivariate logistic regression. Age, sex, length of ICU stay, and variables were statistically significant in the tests and were included in the multivariate analysis. OR: odds ratio; CI: confidence interval; ICU: intensive care unit; BUN: blood urea nitrogen; PTT: partial thromboplastin time; LB: lactate and bilirubin.

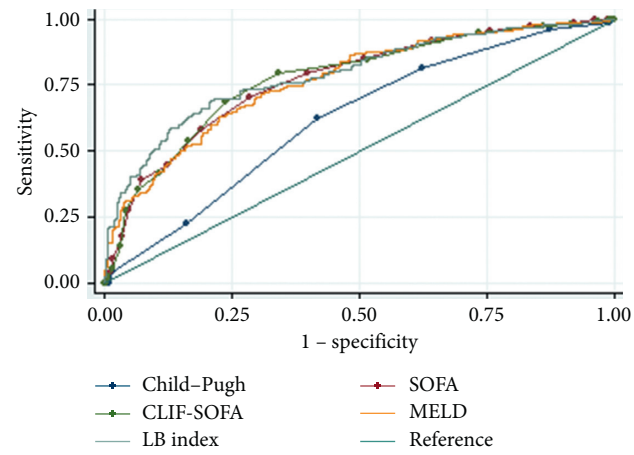

Figure 1: Area under the receiver operating characteristic curve of the scoring systems in predicting 28-day mortality in critically ill patients with cirrhosis. SOFA, sequential organ failure assessment; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; MELD, model for end-stage liver disease; LB: lactate and bilirubin.

liver cirrhosis [6]. SOFA was an effective predictor of mortality in patients admitted to ICU [27]. CLIF-SOFA performed well in predicting 6-month mortality in critically ill cirrhotic patients [11]. The MELD score was used to predict survival in patients with end-stage liver disease [9].

Lactate can be measured in critically ill patients to evaluate the severity of disease [28–30]. Lactate metabolism in cirrhotic patients was significantly different from that in patients without liver damage, leading to a net increase in lactate levels [14, 31]. Increased lactate levels were associated with poor outcome in cirrhotic patients admitted to ICU [17, 32, 33]. The total bilirubin was a significant indicator of liver function. Total bilirubin level was included as an indispensable factor in MELD, Child–Pugh, SOFA, and CLIF-SOFA scores. Thus, we proposed the LB index, a new indicator to predict critically ill cirrhotic patients' prognosis and externally validated it's ability. As our research finally demonstrated, the LB index was an independent predictive factor of poor prognosis of cirrhotic patients.

The laboratory-based LB index has its unique advantages. Through noninvasive blood testing, these values can be readily obtained and objectively evaluated. Besides, compared to other scoring systems built for cirrhotic patients, the LB index can be easily and rapidly calculated at patients' bedside using a simple and convenient formula. Moreover, despite its simplicity, this clinical indicator still

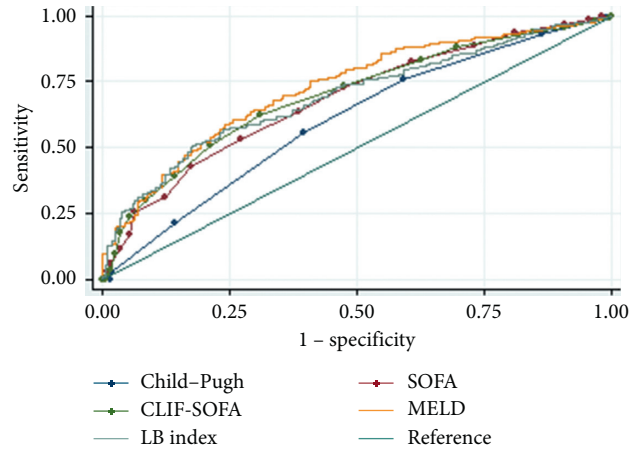

Figure 2: Area under the receiver operating characteristic curve of the scoring systems in predicting 3-year mortality in critically ill patients with cirrhosis. SOFA, sequential organ failure assessment; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; MELD, model for end-stage liver disease; LB: lactate and bilirubin.

Table 4: Diagnostic accuracy of different scoring systems in predicting 28-day mortality at the optimal cutoff point.

Prognostic models	AUROC (95% CI)	*P* value	Cutoff point	Sensitivity	Specificity	PPV	NPV	PLR	NLR
LB index	0.791 (0.747–0.836)	—	6.18	0.70	0.79	0.61	0.84	3.24	0.39
Child–Pugh	0.624 (0.574–0.674)	<0.001	11	0.63	0.58	0.42	0.76	1.50	0.64
SOFA	0.771 (0.727–0.816)	0.372	10	0.70	0.72	0.55	0.83	2.48	0.42
CLIF-SOFA	0.775 (0.731–0.820)	0.455	10	0.80	0.66	0.53	0.87	2.33	0.31
MELD	0.768 (0.723–0.813)	0.271	18	0.72	0.69	0.53	0.83	2.32	0.40

DeLong test was used to compare the AUC between LB index and other clinical models. AUROC: area under the receiver operating characteristic curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; LB: lactate and bilirubin; SOFA: sequential organ failure assessment; CLIF-SOFA: chronic liver failure-sequential organ failure assessment; MELD: model for end-stage liver disease.

Table 5: Diagnostic accuracy of different scoring systems in predicting 3-year mortality at the optimal cutoff point.

Prognostic models	AUROC (95% CI)	*P* value	Cutoff point	Sensitivity	Specificity	PPV	NPV	PLR	NLR
MELD	0.726 (0.680–0.771)	—	18	0.61	0.74	0.76	0.58	2.36	0.53
Child–Pugh	0.602 (0.552–0.652)	<0.001	10	0.76	0.41	0.64	0.55	1.28	0.59
SOFA	0.683 (0.635–0.730)	0.045	10	0.53	0.73	0.73	0.53	1.97	0.64
CLIF-SOFA	0.698 (0.651–0.744)	0.136	10	0.63	0.69	0.73	0.58	2.02	0.54
LB index	0.694 (0.648–0.741)	0.159	6.18	0.51	0.82	0.79	0.55	2.88	0.59

DeLong test was used to compare the AUC between MELD score and other clinical models. AUROC: area under the receiver operating characteristic curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; MELD: model for end-stage liver disease; SOFA: sequential organ failure assessment; CLIF-SOFA: chronic liver failure-sequential organ failure assessment; LB: lactate and bilirubin.

has good prediction accuracy. The LB index can rapidly evaluate the severity of liver cirrhosis and show optimal discrimination ability to predict short-term prognosis in critically ill cirrhotic patients. In our research, we also compared the ability of several scoring systems including the LB index to predict both short- and long-term mortality in critically ill cirrhotic patients. The MELD score performed well in predicting both short- and long-term prognosis. Lactate can improve prediction of short-term mortality in critically ill patients with cirrhosis while its predictive value regarding long-term mortality requires further investigation [19]. The LB index was associated with lactate level, which may lead to the poor performance of LB index in predicting long-term mortality compared with its value in predicting short-term mortality. All need further study.

There are some potential clinically relevant applications of the new LB index. Cirrhotic patients with an LB index more than 6.18 have severely impaired liver function and a high risk of short-term death. An LB index more than 6.18 could be used as an indication for liver transplantation. It has been reported that the prognosis of cirrhotic patients with hepatocellular carcinoma (HCC) and the outcome of HCC treatments is linked to the appropriate assessment of liver function because some standard therapies could indirectly damage nontumoural liver parenchyma leading to hepatic decompensation [34, 35]. Only a few patients with

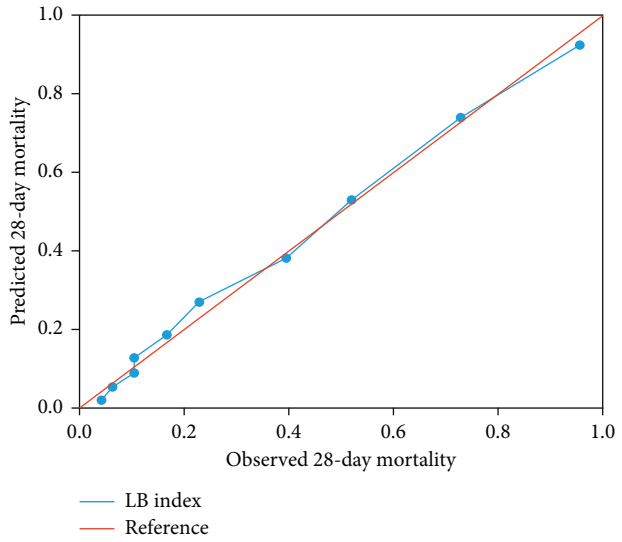

Figure 3: Calibration curve of the LB index for 28-day mortality. LB: lactate and bilirubin.

hepatocellular carcinoma in the Child–Pugh B class can benefit from liver transplantation and whether others will benefit from limited treatment option except liver transplantation remains uncertain [36], but a better definition of liver function by other prognostic scores such as ALBI grade can be useful to better select patients potentially suitable for HCC treatments [37–39]. The LB index could be a new adjunctive parameter to help patient selection. Further studies are needed to provide more useful information on this subject.

However, a few potential limitations of the research need our considerations. First, the research was a retrospective research, which was carried out in a single institution. Second, this study's mortality was defined as all-cause mortality, and other factors of death may affect critically ill cirrhotic patients' mortality. Finally, part of general ICU scoring systems and classic liver-specific scoring systems were included, but others were excluded. Problems will be addressed in our following studies.

5. Conclusions

The laboratory-based LB index performs well in predicting critically ill cirrhotic patients' short-term prognosis, while, for long-term prognosis, the MELD scoring system is more appropriate. In addition, the new LB index may have many potential clinically relevant applications, which need us to further explore and verify.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Xiao-Fu Chen, Yuan Zhao, Wei-Zhen Chen, and Zhi-Ming Huang put forward the research plan; Xiao-Fu Chen, Yuan Zhao, Wei-Zhen Chen, and Xin-Tian Shao were involved in data collection and analysis; Xiao-Fu Chen, Yuan Zhao, and Xin-Tian Shao wrote the manuscript; Xiao-Fu Chen, and Zhi-Ming Huang were involved in critical review and revision of the manuscript. All the authors made their own contributions and agreed to submit the manuscript.

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