Serum lactate level predicts 6-months mortality in hospitalized patients with decompensated cirrhosis

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Background The prediction of prognosis is an important part of management in decompensated cirrhosis (DeCi) patients with high long-term mortality. Lactate is a known predictor of outcome in critically ill patients. The aim of this study was to assess the prognostic value of lactate in DeCi patients.

Methods We performed a single-center, observational, retrospective study of 456 DeCi patients extracted from hospitalization. Univariate and multivariate analyses were used to determine whether lactate was independently associated with the prognosis of DeCi patients. The AUROC was calculated to assess the predictive accuracy compared with existing scores.

Results Serum lactate level was significantly higher in nonsurviving patients than in surviving patients. Univariate and multivariate analyses demonstrated that lactate was a risk-independent factor 6-months mortality (odds ratio: 1.412, P=0.001). ROC curves were drawn to evaluate the prediction efficiencies of lactate for 6-months mortality (AUROC: 0.716, P<0.001). Based on our patient cohort, the new scores (MELD+lactate score, Child-Pugh+lactate score) had good accuracy for predicting 6-months mortality (AUROC=0.769, P<0.001; AUROC=0.766, P<0.001). Additionally, the performance of the new scores was superior to those of existing scores (all P < 0.001).

Conclusion Serum lactate at admission may be useful for predicting 6-months mortality in DeCi patients, and the predictive value of the MELD score and Child-Pugh score were improved by adjusting lactate. Lactate should be part of the rapid diagnosis and initiation of therapy to improve clinical outcome.
**Key word:** Decompensated cirrhosis; lactate; Prognosis

**Introduction**

Liver cirrhosis has a high morbidity and mortality and leads to 1.03 million deaths per year, making it the 14th most common cause of death worldwide(1). In China, survival with cirrhosis is even less optimistic because many hepatitis B- and hepatitis C-infected patients progress to cirrhosis without effective antiviral therapy(2, 3). However, compensated cirrhosis is not easy to detect, and most patients are diagnosed with decompensated cirrhosis (DeCi) in the hospital because of cirrhosis complications such as ascites, gastrointestinal hemorrhage, hepatic encephalopathy, and hepatorenal syndrome. The 1-year mortality of liver cirrhosis varies greatly, from 1% to 57%, according to the complications of DeCi(4). Decompensated cirrhosis carries a poor prognosis because the median survival time is about 2 years, and it imposes a heavy burden on health-care costs, mainly due to the need for repeated hospital admissions(5). Although liver transplantation can significantly improve survival, it is not widely applied due to shortcomings in liver sources, costs, and technology(6). Therefore, it is necessary to use prognostic models to identify high-risk patients. Severity scores have been developed for DeCi patients admitted to the hospital or Intensive Care Unit (ICU) based on combinations of prognostic indicators(7-11). The Child–Pugh and end-stage liver disease (MELD) scores have been widely used to predict the outcomes of cirrhotic patients, but they have obvious deficiencies(12-15). Therefore, a simple and practicable parameter is necessary to boost the predictive efficiency of scores and to guide the choice of therapeutic measures.

Elevated lactate levels may be due to anaerobic metabolism and oxidative stress, in which case it is a marker of tissue hypoxia, or metabolic changes due to stress reactions by the release of epinephrine(16). A previous study indicated that higher lactate levels and reduced lactate clearance are associated with mortality in critically ill patients, especially in septic patients(17, 18). Sepsis and infections are common reasons for hospital admission in DeCi patients in China and are associated with poor outcomes(19). Lactate levels may be a useful tool for assessing the severity of disease in critically ill patients with cirrhosis admitted to the ICU. In a recent report, lactate levels and clearance were independently associated with short-term mortality in critically ill patients with liver cirrhosis, and the lactate-adjusted score was significantly better than the existing scoring system(11). However, the study
populations have been dominated by Caucasians in Europe and the United States, and the most common cause of liver cirrhosis is alcohol. In the national population of cirrhosis caused by viral hepatitis, whether lactate levels can also serve as a prognostic indicator for DeCi patients is still unknown. The aim of this study was to assess the prognostic performance of lactate levels for 6-months mortality in DeCi patients admitted to the hospital in China to guide clinical practice.

Patients and methods

Study design
This was a single-center, retrospective, observational cohort study conducted at a large tertiary public hospital in South China between January 2014 and December 2018. The study protocol was approved by the institutional ethics committee of First Affiliated Hospital of Nanchang University. Informed written consent was obtained from all the study participants.

Study population and setting
The study cohort included all patients aged ≥ 18 years with cirrhosis of the liver who were hospitalized due to any of the hepatic decompensations. Refusal to give consent, age <18 years, pregnancy, cerebrovascular disease, cardiovascular disease, hematologic disorders, and renal failure were exclusion criteria. Patients admitted for specific reasons (i.e. cirrhosis patients with hepatocellular carcinoma admitted for TACE, cirrhosis patients admitted for conditions unrelated to liver cirrhosis). All patients were treated following accepted recommendations and guidelines after admission to the hospital, and they were followed up until death or 6 months(20, 21).

Definitions.

The presence of DeCi was diagnosed according to clinical, biochemical, and radiological parameters; the presence of ascites, hepatic encephalopathy (HE), and/or signs of portal hypertension; ultrasonography; variceal bleeding; and even histology at hospital admission. Hepatic encephalopathy (HE) and acute-on-chronic liver failure (ACLF) were diagnosed according to West Haven criteria, well-established criteria defined by the CLIF Consortium.
Hepatorenal syndrome (HRS) and ascites were diagnosed using the criteria proposed by the International Ascites Club and American Association for the Study of Liver Disease (22-24). The Child-Pugh score was calculated according to TBIL, albumin, international normalized ratio (INR), ascites status, and degree of HE. The MELD score was calculated using the formula: 3.78 x Ln (TBIL μmol/L) + 11.2 x Ln (INR) + 9.57 x Ln (creatinine μmol/L) + 6.43 × (constant for liver disease etiology =0, if cholestatic or alcoholic, otherwise =1).

Study protocol
Patients were enrolled in the study when they were hospitalized with decompensated cirrhosis. During the index hospitalization, data were collected and compiled regarding demographic profile, history, clinical features, presence of other comorbidities, etiology of the cirrhosis, type of decompensation, number of complications, and blood laboratory parameters at admission (white blood cell count (WBC), platelets (PLT), serum sodium (Na), creatinine (Cr), serum urea, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) from venous blood; lactate, oxygenation index (PaO₂/FiO₂) from arterial blood). Patients were followed for 6 months to calculate survival using liver clinic records, institutional medical records or telephone conversations. Patients with incomplete follow-up were not included in the final analysis.

Statistical analysis.
Statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL), and receiver operating characteristic (ROC) analysis was done by using MedCalc statistical software version 15.2.1 (MedCalc, Ostend, Belgium). Continuous and categorical variables were initially described as median (interquartile range [IQR]) and frequency (percentage [%]), respectively. Continuous variables were compared using the Mann–Whitney U-test, and categorical variables were compared using the chi-squared test or Fisher’s exact test. Multivariate analysis was employed to demonstrate the independent predictors for the mortality rate of patients with DeCi. All variables that were found to be associated with mortality (P<0.10) were included as candidate variables in a forward conditional stepwise logistic regression analysis to identify independent predictors for the prognosis of DeCi patients. The diagnostic accuracy of prognostic variables was examined by receiver operating characteristic (ROC) analysis with comparisons between areas under the ROC curves.
(AUROC), done with the De Long test. Sensitivity and specificity were determined using the cut-off point with the highest Youden index (sensitivity +specificity −1). All statistical tests were two-sided, and a value of p < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 405 patients hospitalized with DeCi from January 2014 to December 2018 in this retrospective study. Patient age ranged from 25 to 86 years (median: 53.5 years). The majority of the patients were male (302/456, 74.6%). Demographic and biochemical characteristics of the study population are outlined in Table 1. The predominant etiology of liver cirrhosis was hepatitis, in 62.0% of patients (251/405), followed by alcoholic (14.8%) and cryptogenic cirrhosis (8.4%). The most common decompensation events responsible for hospitalization were gastrointestinal hemorrhage (61.2%), infection (23.2%), hepatic encephalopathy (8.1%), and ascites (7.4%). The average length of hospital stay was 10 (8-12) days. Sixty-eight patients (16.7%) received treatment in the intensive care unit (ICU), and 337 (83.2%) patients received treatment in the general ward. A total of 298 patients had been followed up to 6 months, including 84 patients who died. The causes of death were as follows: 15 (17.9%) from respiratory failure, 39 (46.4%) patients from hemorrhagic shock, 9 (10.7%) patients from hepatic encephalopathy, 8 (9.5%) patients from infectious shock, 5 (5.9%) patients from hepatorenal syndrome, 4 (4.8%) patients from liver failure, and 4 (4.8%) patients from uncertain causes. The baseline characteristics of this cohort are presented in Table 1.

Association between mortality and clinical or laboratory characteristics.

The clinical and laboratory characteristics of these patients are listed in Table 2. DeCi patients were divided into nonsurviving (n=84) and surviving groups (n=214) according to 6-month survival outcomes. The majority of nonsurvivors had been graded higher, as reflected by ALT, AST, bilirubin, GGT, creatinine, INR, PTA, WBC, Lac, Child-Pugh score, and MELD score. However, albumin levels were lower in nonsurvivors. No significant differences in platelet, serum Na, MAP, or PO2/FiO2 were detected.
Univariate and multivariate analysis for 6-months mortality in DeCi patients

When index hospitalization variables were compared, univariate logistic regression analysis showed that >50 years of age, cryptogenic cirrhosis, 3rd-degree ascites, Hepatocellular carcinoma (HCC), ALT, AST, bilirubin, GGT, creatinine, INR, PTA, WBC, Lactate, Child-Pugh score, and MELD score were risk factors and albumin was a protection factor for 6-months mortality in patients with DeCi. Multivariate logistic regression analysis identified that >50 years of age, HCC, GGT, creatinine, and Lactate were risk factors and albumin was a protective factor for 6-months mortality in patients with DeCi. No significant effect was noted for sex, cause of hospitalization, ACLF, acute renal injury, platelets, serum Na, mean arterial pressure, or PaO$_2$/FiO$_2$.

Predictive value for 6-months mortality in DeCi patients

Figure 1 shows the performance analysis of the discriminative accuracy of Lac for 6-months mortality with AUROC of 0.716 (95% CI: 0.649-0.784, P<0.001). The AUROC of MELD score and Child-Pugh score were 0.723 (95% CI: 0.654-0.791, P<0.001) and 0.679 (95% CI: 0.613-0.744, P<0.001), respectively. The ROC curves and comparison of prognostic scores are shown in Figure 1 and Table 4, respectively.

Predictive value of MELD score and Child-Pugh score are improved by adjusting lactate

To improve the predictive value, new scores (MELD+ lactate score, Child-Pugh+ lactate score), created by adding lactate to the MELD score and Child-Pugh score, were established. In the same dataset, an analysis of AUROC at 6-months mortality showed that MELD+ lactate score and Child-Pugh+ lactate score were superior to MELD score and Child-Pugh score, respectively (difference between areas=0.045, 95% CI= 0.017-0.073, Z=3.191, P=0.001; difference between areas=0.087, 95% CI= 0.043-0.131, Z=3.874, P<0.001). The ROC curve and comparison of prognostic scores are shown in Figure 2 and Table 5, respectively.

Discussion

Assessment of prognosis, especially in patients with cirrhosis at the
hospital, is of crucial importance to guide therapeutic measures. To our knowledge, this is the most comprehensive study to evaluate the diagnostic accuracy of MELD score and Child–Pugh score in patients with liver cirrhosis. As we expected, MELD score and Child-Pugh score were associated with 6-months prognosis in the univariate analysis, and multivariate logistic regression also identified that albumin and creatinine, which are parameters of the MELD score, as predictive factors for 6-months mortality. The ROCs of the MELD score and Child-Pugh score were drawn, and the AUROC of those scores was 0.723 and 0.679, respectively. However, they have had obvious deficiencies in previous studies. First, ascites and hepatic encephalopathy, included in the Child–Pugh score, are subjective and may vary according to the physicians’ judgment and the use of diuretics and lactulose. Second, INR, which is one component of both Child-Pugh and MELD scores, does not sufficiently reflect coagulopathy and consequently liver function in liver cirrhosis. Third, there is an interlaboratory variation in INR value. Most studies on the MELD score and Child-Pugh score have been done in Western countries, where the main cause of cirrhosis is alcohol. However, in this study, virus hepatitis-related cirrhosis and gastrointestinal bleeding, which account for most of the cirrhotic population in China, may reduce the prediction efficiency of the score. Therefore, it is meaningful to find a simple and practicable indicator to increase predictive efficiency of score to guide clinical treatment.

Serum lactate levels, being closely associated with tissue hypoxia and anaerobic metabolism, are additionally strongly correlated with death. Various studies provide considerable evidence for the prognostic value of lactate in critically ill patients. Hyperlactemia at the time of admission to the hospital has been proposed to be a potential marker for postoperative morbidity and mortality with a high sensitivity and specificity for adverse effects. Serum lactate levels are currently used in risk stratification of patients with sepsis, trauma and pulmonary embolism. Several studies have revealed that the lactate level has been associated with mortality among patients admitted to the ICU in cirrhotic patients. Andreas Drolz’s study revealed that lactate appropriately reflected the severity of disease and organ failure and was independently associated with short-term mortality in critically ill patients with liver cirrhosis after nearly one year of follow-up, and the performance of chronic liver failure consortium acute-on-chronic liver failure score (CLIF-C ACLFs) was significantly improved by adjusting lactate. Adnan Tas’s multinational research has revealed that the lactate level and acute
Physiology and Chronic Health Evaluation (APACHE II) score are the two best predictive factors of short-term mortality in cirrhotic elderly patients admitted to the ICU(37). However, their study populations were dominated by Caucasians in Europe and the United States, and most cases of liver cirrhosis in those populations are caused by alcohol. In Zhou XD’s study of 949 critically ill cirrhotic patients with acute respiratory failure, a new score (ARF-CLIF-SOFA) score contained serum lactate and had better accuracy for predicting 30-days, 90-days and 1-year mortality compared to the MELD score and Chronic liver failure - sequential organ failure assessment (CLIF-SOFA) score(38). Sun DQ’s research revealed that elevated serum lactate levels were associated with a higher mortality rate in critically ill patients with cirrhosis with acute kidney injury (AKI)(39). However, their study did not clearly reveal that lactate levels were associated with prognosis in decompensated cirrhosis patients in China. Therefore, we designed and completed the study reported here. Our study was a single-center, large sample, observational retrospective analysis that evaluated simple laboratory parameters as predictors of mortality in DeCi patients. This paper aimed to validate the predictive value of lactate for 6-month mortality in compensated cirrhosis (DeCi) admitted to the hospital. First, we found that lactate was significantly higher in nonsurviving patients than in surviving patients (Table 2) and served an independent risk factor for long-term mortality in univariate and multivariate analysis (Table 3). More importantly, our results indicated that lactate was able to predict long-term mortality in DeCi patients (Table 4, and Figure 1) and that the AUROC of the new scores (MELD+ lactate score, Child-Pugh+ lactate score) were higher than those of the MELD score and Child-Pugh score, respectively, based on the same data (Table 4, and Figure 1). Our findings demonstrate that lactate is also a good and independent predictor of long-term outcomes in DeCi patients of the Chinese population, whose cirrhosis is mainly caused by viral hepatitis.

The underlying mechanisms by which serum lactate can predict the prognosis of patients with DeCi are not well defined. Lactate is considered the main end-product of anaerobic glycolysis (Embden–Meyerhof pathway), where nicotinamide adenine dinucleotide is regenerated by the glycolytic lactate dehydrogenase system upon redox-coupled reduction of pyruvate to lactate(40). Approximately ~1500 mmol of lactate is produced daily in the human body, primarily by highly glycolytic tissues(41). Traditionally, lactate has been deemed a marker for tissue hypoxia, and the generation and consumption of lactate are strictly balanced in physiological...
conditions. Hyperlactatemia is usually the result of either increased lactate production or reduced consumption (42). The liver is responsible for up to 70% of whole-body lactate clearance, especially hepatic impairment, which is associated with increased lactate levels due to impaired mitochondrial oxidation (43). Another source of hyperlactatemia is increased lactate production, which is related to microcirculatory oxygen imbalance (41). Patients with unstable hemodynamics demonstrate increased ketone/pyruvate ratios and decreased arterial ketone body ratios related to anaerobic production. Previous studies revealed that in the absence of circulatory delivery relative to systemic metabolic demand, microcirculatory processes hampering oxygen utilization at the tissue level may raise lactate levels (44). Circulatory failure is also considered a complication related to mortality in critically ill cirrhotic patients (45). Furthermore, mechanisms other than tissue hypoxia can account for hyperlactatemia, such as drugs and intoxicants and pyruvate dehydrogenase dysfunction (46). Hence, we assume that the relationship between blood lactate and prognosis of DeCi patients is the result of comprehensive effects on metabolism and microcirculation.

This study has several limitations. First, as a single-center, retrospective cohort study, the study may have inherent limitations, and some patients were lost to follow-up, which may have resulted in selection bias. The findings need to be confirmed in large, multicenter, prospective studies. Second, we were not able to evaluate the predictive role of dynamic changes of lactate, as the long-term changes in serum lactate and lactate clearance were not routinely measured in clinical practice. Finally, organ failure-related scores, such as SOFA score and CLIF-C ACLFs, were not calculated, and the correlation between these scores and lactic acid was not analyzed.

In conclusion, many factors may be useful as a predictor of mortality in the hospital in patients with DeCi, including MELD score and Child-Pugh score. Our results indicate that initial lactate concentration strongly and independently predicts long-term outcomes. In terms of prognostic value, lactate levels demonstrate a similar discriminatory power as the MELD score and Child-Pugh score, and the predictive efficiency of those existing scores is elevated by adding lactate. From a clinical perspective, using lactate might be more convenient, as fast diagnosis and initiation of therapy are essential in reducing mortality.

**Figure 1** Receiver operating characteristic curves of Lactate, MELD score, Child-Pugh score. MELD: the model for end-stage
liver disease score; Child-Pugh: the Child-Pugh score.

Figure 2 Comparing the receiver operating characteristic curves of the scores. MELD: the model for end-stage liver disease score; Child-Pugh: the Child-Pugh score. (A) ROC for MELD score vs MELD+lactate score; (B) ROC for Child-Pugh score vs Child-Pugh+lactate score.

Author Contributions
YZ and YN contributed equally to this study. YZ and YN designed and wrote the manuscript. SZW collected the data, CL analysed the data, XZ critically revised the manuscript.

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Conflict of Interest statement: The authors declare that there are no conflicts of interest.

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