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An integrated MELD model improves short-term prognosis of HBV-related acute-on-chronic liver failure

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Abstract:

AIM

To investigate whether the short-term prognosis of HBV-related acute-on-chronic liver failure (ACLF) could be improved by using an integrated MELD model including serum lactate.

METHODS

This clinical study was conducted on the First Affiliated Hospital, Fujian Medicine University, China. From 2009 to 2015, 236 patients diagnosed with HBV-related ACLF in our center were recruited in this 3-month follow-up study. Demographic data and serum lactate level were collected. The end-stage liver disease (MELD) scores with or without serum lactate level from survival and non-survival groups were recorded and compared.

RESULTS

236 patients with HBV-ACLF were divided into 2 groups, namely survival group (S) and non-survival group (NS). Compared with non-survival group, The patients in survival group had a significant lower level of serum lactate (3.11 ± 1.98 vs 4.67 ± 2.43 , $t = 5.43$, $P < 0.001$) and MELD scores (23.33 ± 5.42 vs 30.37 ± 6.58 , $t = 9.01$, $P = 0.023$). Furthermore, serum lactate level was found in a positive correlation with MELD score ($r = 0.315$, $P < 0.001$). Therefore, a modified MELD model including serum lactate was developed by logistic regression analysis ($0.314 \times \text{lactate} + 0.172 \times \text{MELD} - 5.923$). To predict 3-month mortality, the patients from S group have significant lower baseline scores (-0.930 ± 1.34) compared with those from NS group (0.771 ± 1.32 , $t = 9.735$, $P < 0.001$) by using MELD-LAC model. The area under the receiver operating characteristic curve (AUROC) was 0.859 calculated by using MELD-LAC

model, which was significantly higher than that calculated by using the lactate level (0.790) or MELD model alone (0.818). When the cutoff value was set at -0.4741, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for predicting the short-term mortality was 91.5%, 80.10%, 94.34% and 74.62%, respectively. When the MELD-LAC scores at baseline level were set at -0.5561 and 0.6879, the corresponding mortality within 3 month were 75% and 90%, respectively.

CONCLUSION

The short-term prognosis of HBV-related acute-on-chronic liver failure (ACLF) was improved by using an integrated MELD model including serum lactate from the present 6-year clinical study.

Keywords: hepatitis B Virus, liver Failure, MELD score, prognosis, serum Lactate level.

Core tip: This is a retrospective study to evaluate the short-term prognosis of HBV-ACLF. 236 patients with HBV-ACLF were divided into 2 groups, namely survival group (S) and non-survival group (NS). To predict 3-month mortality, the patients from S group have significant lower baseline scores compared with those from NS group by using MELD-LAC model. AUROC was 0.859 calculated by using MELD-LAC model, which was significantly higher than that calculated by using the lactate level (0.790) or MELD model alone (0.818). The short-term prognosis of HBV-ACLF was improved by using an integrated MELD model including serum lactate from the present 6-year clinical study.

INTRODUCTION

Hepatitis B virus (HBV) infection is a severe public health problem all over the world. The prevalence of hepatitis B is particularly high in China. HBV-related acute-on-chronic liver failure (ACLF) is a rapidly progressive disease with a

high mortality up to 60%-75%^[1]. The accurate assessment of the disease severity is critical needed, before clinicians make decisions on potential treatments like medication or liver transplantation (LT). The end-stage liver disease (MELD) score model^[2,3] is a well-accepted model for assessing the feasibility of LT, however the accuracy of prediction is still unsatisfied^[4]. A more objective and quantitative model with higher repeatability to predict the short-term prognosis of HBV-related ACLF is urgently needed.

Lactate (LAC) is mainly metabolized in the liver but widely used as an important indicator in organ failure or serious bacterial infection. Hyperlactatemia normally reflects both increased production and impaired clearance in patients with liver dysfunction^[5], and a higher level of LAC always indicates a worse prognosis^[6]. Although several potential hypoxic and non-hypoxic mechanisms have been implicated on the persistent hyperlactatemia and the high level of LAC, the exact role of these parameters has not been specifically addressed in clinical studies^[7,8]. In this study, we investigated the serum LAC level in patients with HBV-related ACLF, and developed an integrated MELD model including serum lactate (MELD-LAC model) to predict the short-term prognosis (3 months) of HBV-related ACLF.

MATERIALS AND METHODS

Patients

393 patients, who were diagnosed with HBV-related ACLF and admitted in our Center, were included in the present clinical study between September 2009 and October 2015. The subjects were aged from 18~65 years old. The diagnosis of ACLF was conducted according to the American Association for the Study of Liver Failure: Update 2011^[9]. Three months after diagnosis, these patients were followed up by telephone. The patients were divided into 2 groups, namely the Survival group (S group) and the non-Survival group (NS group), based on whether they are survival or not post 3 months of admission. The clinical data were collected within the first 24 hours after admission,

including hepatic, renal, and coagulation function, as well as the LAC level. The onset time of hepatic encephalopathy was also noted if it happened. MELD scores were calculated as follows:

$$\text{MELD} = 3.8 \times \ln(\text{TBil}[\text{mg/dL}]) + 11.2 \times \ln(\text{INR}) + 9.6 \times \ln(\text{Cr}[\text{mg/dL}]) + 6.4 \times \text{cause}.$$

Since the ACLF was due to HBV infection, the cause was counted for 1 in this study. On admission, each patient's baseline values of serum LAC level, total bilirubin, creatinine level and prothrombin time-international normalized ratio (PT-INR) were measured. The serum LAC level was measured by using a commercial test kit (Johnson & Johnson Inc., USA) with a normal value of 0.9~2.0 mmol/L. Total bilirubin and creatinine levels were tested by using Olympus Chemistry Analyzer AU2700. All reagents for bilirubin and creatinine tests were purchased from Olympus Corporation (Japan). PT value test and INR calculation were measured by using a Stago STA Compact coagulation analyzer (Diagnostica Stago, French).

Treatment

After HBV-related ACLF was diagnosed, all the patients were treated by standard treatment protocols, including nutritional support, hepatocyte proliferation, prevention of infection, correction of anomalies in the coagulation system and improvement of cerebral edema. In addition, plasmapheresis was also performed when it was necessary. The survival data were collected after 3 months.

Statistical analysis

Data analysis was conducted by using SPSS 17.0 software. The significance of data was tested by the Student's test and the Chi-square test, respectively. The correlation between groups was analyzed by the Pearson's product-moment correlation coefficient test. P value less than 0.05 was considered statistically significant. Logistic regression analysis was used to establish the prognosis model. The prediction accuracies of the newly developed prognosis model

(MELD-LAC model), LAC and MELD scores on predicting the short-term prognosis of HBV-related ACLF patients were assessed by area under the receiver operating characteristic (AUROC) curve.

RESULTS

Demographic Data

A total of 393 serum samples from patient with HBV-related ACLF were collected, 157 samples were excluded from the present study due to the complications of hepatocellular carcinoma, kidney injury, diabetes or alcoholic liver diseases. According to the follow-up results in this 236 enrolled cases, 130 (110 males and 20 females) were recruited into the S group, while 106 (87 males and 19 females) were recruited into the NS group. The 2 groups have no statistical difference on gender or age, but do have significant differences in TBIL, Cr, INR, LAC levels and MELD scores (all $P < 0.05$) (Table 1). There were 68 patients in S group and 57 patients in NS group had received plasmapheresis as an additional enhanced therapy, but it did not provide any positive outcome ($P = 0.896$). No patient in this study had received LT.

82.3% (107 of 130) of patients in S group and 95.2% (101 of 106) of patients in NS group was found to have elevated LAC level of more than 2 mmol/L. A significant difference was found in above percentages between these two groups ($\chi^2 = 9.40$, $P = 0.002$). Furthermore, there were 13.1% of patients (17 of 130) in the S group and 59.4% of patients (63 of 106) in NS group was found to have elevated LAC level of more than 4 mmol/L. A significant difference between the percentages of the S group and the NS group was also found ($\chi^2 = 55.999$, $P < 0.001$). The mean LAC level in S group (3.11 ± 1.98 mmol/L) was significantly lower than that in NS group (4.67 ± 2.43 mmol/L) ($P < 0.001$). In addition, no significantly difference was shown in the CTP scores between the S and NS group ($P = 0.373$), but a significantly difference was shown in the MELD scores between two groups ($P = 0.023$).

Using the Spearman analysis method, the correlations between MELD score/serum LAC levels and the mortality in 3 months were analyzed (Table 2). The results from Pearson's analysis also showed that both serum LAC level and MELD score had a statistically significant correlation with the short-term prognosis of HBV-related ACLF ($r = 0.315$, $p < 0.001$).

Construction of an integrated MELD model including serum lactate

Based on single factor analysis, both MELD score and LAC level were correlated with the 3-month mortality of HBV-related ACLF. The forward logistic regression method was used to establish the MELD-LAC model: $0.314 \times \text{LAC} + 0.172 \times \text{MELD score} - 5.923$ (Table 3). The patients from the S group had significantly lower baseline MELD-LAC scores (-0.930 ± 1.34) compared with those from the NS group (0.771 ± 1.32 , $t = 9.735$, $P < 0.001$).

The short-term prognosis of HBV-related acute-on-chronic liver failure (ACLF) was improved by using an integrated MELD model including serum lactate from the present 6-year clinical study.

Prediction of the short-term prognosis of HBV related ACLF by using MELD-LAC model

To predict the 3-month mortality, the LAC model alone has a very similar positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity compared to the MELD model. Interestingly, the new MELD-LAC model by combining these 2 independent factors, has a better predicting score than that by using these 2 models alone. When the cutoff value of the MELD-LAC model was set at -0.4741 , based on the best Yoden index. Therefore, an AUROC curve of 0.859 (Table 4) was obtained when this equation was applied to evaluate the prognosis, with a sensitivity of 91.5% and a specificity of 80.10% , which were much greater than the other 2 models. Compared the AUROCs obtained from above three models, the prognosis performances were listed as follows: MELD-LAC > MELD > LAC (Figure 1).

From our analysis, the patients with a MELD-LAC score of -0.5561, -0.4741 and 0.6879 respectively, had the 3-month mortality of 75%, 78.86% and 90%, correspondingly. The PPV and NPV of MELD-LAC were 94.34% and 74.62%, which were significant improved compared with the scores obtained from the MELD and LAC model alone.

¹ The patients were divided into 2 groups, when the cutoff value of the MELD-LAC model was set at -0.4741. The first group (MELD-LAC \geq -0.4741) included 123 patients, and 78.86% were dead after 3 months. The second group (MELD-LAC $<$ -0.4741) included 113 patients, and only 11.50% were dead after 3 months. A statistically significant ²⁷ difference was observed between these 2 groups ($X^2 = 107.35$, $p < 0.001$). When comparing with the MELD model with the cutoff value of 25, the MELD-LAC model with cutoff value of -0.4741 were apparently achieved a better prediction on short-term prognosis.

DISCUSSION

¹ ACLF is a severe health problem with a high mortality^[10-12]. In clinical practice, predicting the progression of this disease is the biggest challenge for the clinicians. Currently, 3 scoring systems, namely KCH criteria, ¹ Child-Turcotte-Pugh (CTP) score and MELD score^[13,14] systems, are commonly implemented ¹ to predict the prognosis of ACLF patients; CTP score has been used traditionally to assess the prognosis of cirrhosis instead of ACLF; the MELD scoring system has been developed to assess various liver diseases, including assessing the severity of ACLF of all causes to determine the ideal timing of liver transplantation, as well as providing direct information to make support medical decision^[15]. The MELD scoring system is widely considered to be better than the CTP score, however it does have several limitations, for example the diagnostic sensitivity and specificity of MELD model is not high enough.

In the MELD scoring system, several variables associated with poor

prognosis of ACLF are not considered, including hepatic encephalopathy (HE), infections, and hemorrhage. Therefore, modification for MELD model is needed to improve its outcome in clinical practice. Addition of Na⁺ into the MELD (MELD-Na) has been proposed and has been successfully evaluated as a better score in patients with ascites, but only for those patients with sodium levels below normal. However, such a condition is only presented in 30% of patients with decompensated cirrhosis^[16].

The elevation of lactate level in ACLF situation has been reported and might be attributed to several suggested mechanisms^[17,18]: first of all, the liver is the organ primarily responsible for LAC clearance, and the LAC clearance may be impaired in the presence of severe liver dysfunction; secondly, some ACLF-related complications, e.g. bacterial infection, may also raise the LAC level; last but not least, hypovolemia-related hypoperfusion also very likely to induce an elevation of LAC level during the early pre-resuscitative phase. In fact, some previous studies have shown that the acutely injured liver may act as a source of evaluating LAC ^[19]. Taken together, we suggest that the LAC level could be used as a useful marker for assessing the severity of ACLF. As a simple measure widely available in current hospital system, early measurement of serum LAC can provide important prognostic information in patients with acute variceal haemorrhage requiring ICU admission^[20-22]. But to the best of our knowledge, the LAC level had never been considered as a critical biomarker for prognosis prediction of HBV-related ACLF.

Our results showed that LAC could be treated as a useful tool to assess the situation of HBV-related ACLF. The evaluated LAC level was found in 82.3% of the S group, but 95.2% of NS group ($X^2 = 9.40$, $P = 0.002$). The mean LAC level in S group (3.11 ± 1.98 mmol/L) was lower than that in the NS group (4.67 ± 2.43 mmol/L) ($P < 0.001$). Further analysis showed that the baseline of LAC level was related with patients' prognosis with a rational sensitivity (86.80%). The AUROC for predicting the 3 months mortality based on the LAC model is relatively lower than that from the MELD model (0.79 vs

0.818), which is consistent with previous studies^[22].

In our study, a positive correlation between the LAC and MELD scores was demonstrated, suggesting that a combination of LAC and MELD scores was very likely to increase prediction accuracy for ACLF prognosis. Therefore, we developed an integrated MELD model including serum lactate level to improve the short-term prognosis prediction of HBV-related ACLF by combining 2 parameters together (LAC and MELD). By adopting the forward logistic regression method, LAC and MELD scores were subjected to the equation, to yield a new MELD-LAC model.

The new model showed a better (AUROC = 0.859) prediction score on the prognosis of HBV-related ACLF, when compared with either LAC (0.790) or MELD model (0.818) alone. When the cutoff value was set at -0.4741, the MELD-LAC model had a sensitivity of 91.50% and a specificity of 80.10% for predicting the mortality within 3 month. The patients were further divided into 2 groups according to the above cutoff value. The mortality was 78.86% in the higher score group (MELD-LAC \geq -0.4741) and 7.96% in the lower score group (MELD-LAC < -0.4741), showing a significant difference between these 2 groups ($X^2 = 107.35$, $P = 0.000$). Under such a cutoff value setting (-0.4741), the MELD-LAC model seemed to provide a much more accurate prediction than normal MELD model with a cutoff value of 25 (Table 5). According to our data, 3-month mortality of the patients was 75%, and 90% could be precisely predicted by the scores of MELD-LAC (-0.5561 or 0.6879) on baseline. Our results also showed no difference between the S group and NS group in CTP scores (Table 1), suggesting that CTP system is not a good tool in evaluating the outcome of HBV-related ACLF.

There are some limitations of this study. Our study indicated, for the first time, that an integrated MELD model including serum lactate was a better prediction model for the prognosis of HBV-related ACLF, with higher PPV and NPV. Therefore, further research will be required to combine this model into the classic model or develop a more accurate prognostic model. The

patient population came merely from a single center in this study and it was a retrospective study; further research and verification need to be done in larger multi-center studies.

Serum LAC test was a simple and mature clinical measurement in modern hospitals, and it reflects both direct liver injury and other organ dysfunction. Dynamic monitoring of LAC was able to provide an new opportunity for the clinicians with more accurate disease assessment, prognosis predication and treatment guidance on the early stage of the liver disease. Hereby, we concluded that an integrated MELD model including serum lactate is a better prediction model for the prognosis of HBV-related ACLF, with higher PPV and NPV.

COMMENTS

Background

HBV-related acute-on-chronic liver failure (ACLF) is a rapidly progressive disease with a high mortality up to 60%-75%. The accurate assessment of the disease severity is critical needed, before clinicians make decisions on potential treatments like medication or liver transplantation (LT). The end-stage liver disease (MELD) score model is a well-accepted model for assessing the feasibility of LT, however the accuracy of prediction is still unsatisfied. A more objective and quantitative model with higher repeatability to predict the short-term prognosis of HBV-related ACLF is urgently needed.

Research frontiers

In the MELD scoring system, several variables associated with poor prognosis of ACLF are not considered, including hepatic encephalopathy (HE), infections, and hemorrhage. Therefore, modification for MELD model is needed to improve its outcome in clinical practice. Addition of Na⁺ into the MELD (MELD-Na) has been proposed and has been successfully evaluated as a better score in patients with ascites, but only for those patients with sodium

levels below normal. However, such a condition is only presented in 30% of patients with decompensated cirrhosis.

Innovations and breakthroughs

Lactate (LAC) is mainly metabolized in the liver but widely used as an important indicator in organ failure or serious bacterial infection. Hyperlactatemia normally reflects both increased production and impaired clearance in patients with liver dysfunction, and a higher level of LAC always indicates a worse prognosis. Although several potential hypoxic and non-hypoxic mechanisms have been implicated on the persistent hyperlactatemia and the high level of LAC, the exact role of these parameters has not been specifically addressed in clinical studies. In this study, we investigated the serum LAC level in patients with HBV-related ACLF, and developed an integrated MELD model including serum lactate (MELD-LAC model) to predict the short-term prognosis (3 months) of HBV-related ACLF.

Applications

This study developed an integrated MELD model including serum lactate level to improve the short-term prognosis prediction of HBV-related ACLF by combining 2 parameters together (LAC and MELD).

Terminology

LAC: lactate. MELD: model for end-stage liver disease.

MELD-LAC model: A prediction accuracies of the newly developed prognosis model by combining 2 parameters together (LAC and MELD).

Peer-review

The author of this paper evaluated the efficacy of the short-term prognosis of HBV-related acute-on-chronic liver failure (ACLF) was improved by using an integrated MELD model including serum lactate from the present 6-year

clinical study. The new model showed a better prediction score on the prognosis of HBV-related ACLF, when compared with either LAC or MELD model alone.

Table 1 Demographic data, biochemical factors , clinical and surgical characteristics from S group and NS group

| Groups | S (n= 130) | NS (n = 106) | <i>t or t'</i> | <i>P</i> |
|--------------------------|----------------------|----------------------|----------------|--------------|
| Age (yr) | 43.51±14.13 | 45.97±10.69 | 1.48 | 0.140 |
| Male/Female (n) | 110/20 | 87/19 | 0.273 | 0.363 |
| Liver cirrhosis (n,%) | 63(48.46) | 68(64.15) | 5.82 | 0.011 |
| TBil (μmol/L) | 344.85±160.82 | 456.63±180.43 | 5.04 | <0.001 |
| ALT | 92.62±82.80 | 101.84±83.71 | 0.847 | 0.389 |
| AST | 92.81±91.84 | 103.86±79.20 | 0.978 | 0.329 |
| GLO | 27.72±8.95 | 27.84±8.85 | 0.1 | 0.92 |
| WBC | 8.27±4.12 | 8.21±4.29 | -0.117 | 0.907 |
| PCT | 0.53±0.29 | 0.58±0.54 | 0.886 | 0.377 |
| Ammonia | 67.29±35.55 | 69.03±47.57 | -0.312 | 0.755 |
| INR | 2.46±0.97 | 3.11±1.63 | 3.733 | <0.001 |
| Cr (μmol/L) | 79.31±45.25 | 99.80±88.74 | 2.293 | <0.001 |
| CHE (U/L) | 3956.30±1377.54 | 3529.00±1509.89 | 0.17 | 0.859 |
| Alb (g/L) | 31.22±3.98 | 30.99±3.96 | -0.428 | 0.398 |
| DNA | 594275±230160 | 425886±110810 | -0.691 | 0.491 |
| LAC (mmol/L) | 3.11±1.98 | 4.67±2.43 | 5.43 | <0.001 |
| <2.68 | 76 | 14 | 50.685 | 0.000 |
| 2.68~4 | 37 | 29 | 0.035 | 0.484 |
| ≥4 | 17 | 63 | 55.999 | <0.001 |

| | | | | |
|----------------|------------|------------|-------|-------|
| CTP | 10.54±1.63 | 10.74±1.73 | 0.892 | 0.373 |
| MELD score | 23.33±5.42 | 30.37±6.58 | 9.01 | 0.023 |
| Plasmapheresis | 68 | 57 | 0.05 | 0.896 |

TBil: total bilirubin; Cr: creatinine; INR: international normalized ratio for prothrombin time; MELD: model for end-stage liver disease; LAC: the venous lactate; ALB: albumin; GLO: globulin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CHE: cholinesterase; WBC: white blood cell; PCT: procalcitonin; CTP: Child-Turcotte-Pugh score.

Table 2 Factors correlated to prognosis of HBV-related ACLF

| Factors | Correlation index | P |
|---------|-------------------|--------|
| MELD | 0.548 | <0.001 |
| LAC | 0.499 | <0.001 |
| TBIL | 0.308 | <0.001 |
| INR | 0.289 | <0.001 |
| Cr | 0.014 | 0.828 |
| Alb | 0.071 | 0.273 |
| CHE | 0.058 | 0.373 |

TBil: total bilirubin; Cr: creatinine; INR: international normalized ratio for prothrombin time; MELD: model for end-stage liver disease; LAC: the venous lactate; ALB: albumin; CHE: cholinesterase.

Table 3 The regression coefficients and indices of the MELD-LAC model

| Index | β | SE | Wald | df | P value | Exp(β) |
|----------|---------|-------|--------|----|---------|----------------|
| MELD | 0.172 | 0.028 | 37.198 | 1 | 0.000 | 1.188 |
| LAC | 0.314 | 0.098 | 10.195 | 1 | 0.001 | 1.368 |
| Constant | -5.923 | 0.824 | 51.724 | 1 | 0.000 | 0.003 |

MELD: model for end-stage liver disease; LAC: the venous lactate.

Table 4 Prognostic values of the various models

| models | AUROC | 95% CI | Cut-off value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|----------|-------|-------------|------------------|--------------------|--------------------|------------|------------|
| MELD | 0.818 | 0.759-0.877 | 24.5 | 87.70 | 63.80 | 85.85 | 64.62 |
| LAC | 0.790 | 0.730-0.850 | 2.68 | 86.80 | 62.10 | 86.79 | 58.46 |
| MELD-LAC | 0.859 | 0.807-0.911 | -0.4741 | 91.5 | 80.10 | 94.34 | 74.62 |

AUROC: the area under the receiver operating characteristic; PPV: positive predictive value; NPV: negative predictive value.

Table 5. Comparison of predicting performance of the MELD-LAC and MELD model

| Groups | | Non-survival | Survival | X ² , P value |
|----------|--------------------|--------------|----------|--------------------------|
| MELD | MELD < 25 | 16 | 83 | 56.98, < 0.001 |
| | MELD ≥ 25 | 90 | 47 | |
| MELD-LAC | MELD-LAC < -0.4741 | 13 | 100 | 107.35, < 0.001 |
| | MELD-LAC ≥ -0.4741 | 97 | 26 | |

Figure 1 AUROC of the MELD-LAC, LAC and MELD score models.

MELD: model for end-stage liver disease; LAC: the venous lactate.

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