Plasma concentration of diamine oxidase (DAO) predicts 1-month mortality of acute-on-chronic hepatitis B liver failure

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ABSTRACT

Background: Acute-on-chronic hepatitis B liver failure (ACHBLF) has high 1-month mortality but it is difficult to predict. This present study was aimed to determine the diagnostic value of plasma diamine oxidase (DAO) in predicting the 1-month mortality of ACHBLF.
Methods: A total of 106 consecutive newly diagnosed ACHBLF patients were retrospectively collected. The plasma expression of DAO was determined using enzyme-linked immunosorbent assay (ELISA).
Results: The plasma DAO level of survivals [14.0 (7.1; 26.5) ng/mL] was significantly lower than the non-survivals [58.6 (32.5; 121.3) ng/mL, $P < .001$]. The plasma DAO level, hepatic encephalopathy, spontaneous bacterial peritonitis and model for end-stage liver disease (MELD) score were independent factors associated with the 1-month mortality for ACHBLF. The cut-off point of 15.2 ng/mL for plasma DAO level with sensitivity of 95.45%, specificity of 62.5%, 22.6 for MELD score with sensitivity of 90.91%, specificity of 67.5%, 0.07 for DAO plus MELD with sensitivity of 87.88%, specificity of 80% were selected to discriminate 1-month morality of ACHBLF. Furthermore, DAO plus MELD score showed high AUROC than MELD score for predicting 1-month (0.916 vs. 0.843, $P < .01$).
Conclusions: The plasma DAO level plus MELD > 0.07 predicts poor 1-month mortality of ACHBLF.

1. Introduction

Acute-on-chronic liver failure (ACLF) refers to the condition of a rapid worsen of liver function of chronic liver disease, which can develop into serious complications within a short period of time, such as hepatorenal syndrome (HRS) and hepatic encephalopathy (HE) [1]. In China, the incidence of hepatitis B virus (HBV) infection is high and estimated 70% of acute-on-chronic liver failure patients have HBV infection history, which is called ACHBLF [2]. Furthermore, ACHBLF progresses rapidly and has high 1-month mortality. Previous research found that about 50–90% ACHBLF patients were died within 1-month [3,4]. Currently, liver transplantation is the only effective treatment strategy for patients with ACHBLF who cannot improve with supportive measures. However, only very few ACHBLF patients were able to successfully receive a liver transplant, due to a shortage of liver sources and other causes [5]. Therefore, it is very important to accurately identify patients with high mortality at the early stage of ACHBLF. The MELD score is currently the most commonly used model to predict ACHBLF mortality in majority of eastern areas [6,7]. However, it's still

controversial for MELD predicting the short time mortality of ACHBLF, especially 1- month mortality. Therefore, new 1-month forecasting indicators are urgently needed to assess the severity of the identification and prediction of mortality.

The imbalance of intestinal microecology is associated with many diseases [8], such as spontaneous bacterial peritonitis, hepatic encephalopathy, inflammatory bowel diseases, chronic liver disease, liver cirrhosis, and so on [9–11]. The stability of intestinal microecosystem is based on three interrelated components: microflora, mucosal barrier and local immune system [12]. In previous studies, patients with liver cirrhosis and chronic liver disease showed significant disorder in intestinal microecology [13,14]. It is not only associated with significant fecal overgrowth of both Grampositive and negative bacterial species, but also related to the increase of intestinal permeability and the bacterial translocation [15,16]. ACLF refers to the condition of a rapid worsen of liver function of chronic liver disease, Therefore, there is a possibility that ACLF has substantial derangements in the intestinal microecology [17].

The diamine oxidase (DAO) was confirmed as a pleiotropic

circulating biomarker with intestinal mucosal maturation and interity [18,19]. DAO has been proved to be a fast and sensitive biomarker of the intestinal wall permeability and barrier function [20,21]. Currently, the plasma level of DAO has been reported to be associated with the occurrence and prognosis of many diseases, including inflammatory bowel disease, liver cirrhosis, and small-cell carcinoma of the lung [19,22–24]. However, there is no data on the potential for the plasma DAO as a biomarker for predicting the 1-month mortality of ACHBLF. In our present study, we measured the plasma DAO concentration of patients with ACHBLF to determine whether the DAO was related to the outcome of ACHBLF and to evaluate the the diagnosis value of DAO as a biomarker for predicting 1-month mortality of ACHBLF.

2. Methods

2.1. Study design and study population

One hundred and six newly diagnosed ACHBLF patients were retrospectively recruited from January 2014 to October 2016 at the Department of Hepatology, Qilu Hospital of Shandong University. According to the guidelines of the Helsinki declaration, all participants were given written agreement approved by the local Research and Ethics Committee at Qilu Hospital of Shandong University [25]. The selection and exclusion flowchart of ACHBLF patients was shown in Fig. 1.

According to the consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL), ACHBLF was diagnosed as: (1) the presence of serum hepatitis B surface antigen (HBsAg) ≥ 6 months; (2) acute worsening of condition and recent development complications whithin 4 weeks; (3) total bilirubin (TBIL) ≥ 85 μmol/L; (4) plasma prothrombin activity (PTA) ≤ 40% [1,4]. Exclusive criteria was the following:(1) Co-infection with other hepatotropic viruses; (2) history of other liver diseases such as metabolic liver diseases, autoimmune liver diseases; (3) alcohol abuse; (4) pregnant; (5) hepatocellular carcinoma; (6) known decompensated cirrhosis; (7) combine other diseases, such as hyperthyroidism, haematological disorders.

Since ACHBLF patients had the highest mortality rate in 1 month, the study mainly studied the prediction value of DAO for the 1-month
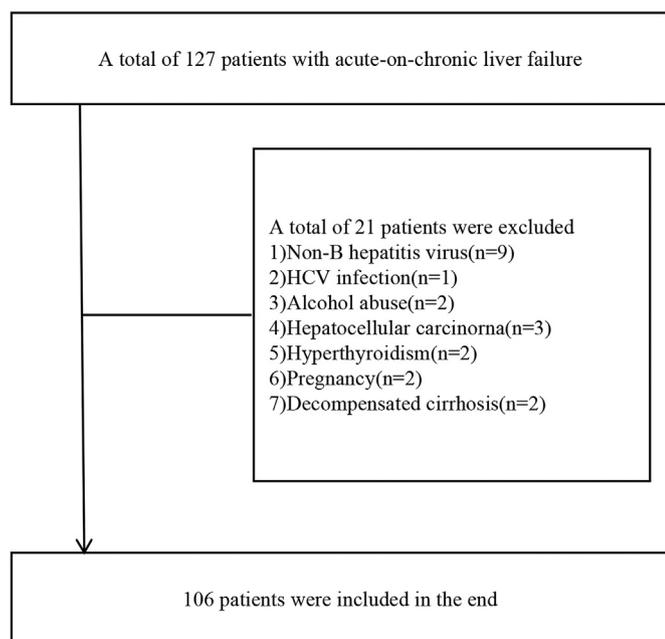

Fig. 1. Flowchart depicting the selection and exclusion process of the participants.

Table 1
Characteristics of ACHBLF patients.

Variables	Survival(n = 40)	Nonsurvival(n = 66)	P value
Male(%)	32(80%)	50(75.8%)	0.613
Age(year)	46(31–54)	49(35–56)	0.120
HBeAg(+),n(%)	29(72.5%)	50(75.8%)	0.080
HBsAg	5560(3090–6107)	6542(5770–7214)	0.980
HBV-DNA(+),n(%)	30(70%)	48(72.7%)	0.800
ALT(IU/L)	175(52–296)	113(72–182)	0.112
AST(IU/L)	98.5(44.5–179)	82(54–112)	0.120
TBIL(μmol/L)	196(151–248)	305(262–385)	0.000
ALB(g/L)	34.2(31.6–37.4)	32.3(30.0–34.7)	0.014
INR	1.9(1.8–2.1)	2.5(2.1–3.7)	0.001
PTA(%)	38(32–39)	30(18–33)	0.001
Cr(μmol/L)	72(65–78)	77(68–87)	0.653
AFP(ng/mL)	156(104–416)	56(39–88)	0.000
MELD score	22.0(20.7–26.5)	27.3(24.8–32.3)	0.000
WBC(10⁹/L)	8.2(5.2–14.8)	7.0(6.2–11.8)	0.961
HGB(g/L)	138(130–140)	129(124–136)	0.056
PLT(10⁹/L)	132(111–173)	129(100–150)	0.013
Na(mmol/L)	137(135–139)	134(128–137)	0.130
SBP[a] (n,%)	2(5%)	36(54.5%)	0.000
Ascites[a] (n,%)	7(17.5%)	38(60.6%)	0.000
HE[a] (n,%)	5(12.5%)	38(57.6%)	0.000

ACHBLF, acute-on-chronic hepatitis B liver failure; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; INR, international normalised ratio; PTA, prothrombin activity; Cr, creatinine; AFP, a-fetoprotein; WBC, white blood cell; HGB, haemoglobin; PLT, platelet; Na, Sodium; MELD scores, model for end-stage liver diseases scores; SBP, spontaneous bacterial peritonitis; HE, hepatic encephalopathy.
Quantitative variables were expressed as the median (centile 25; centile 75).
[a] Categorical variables were expressed as n (%).

mortality, so all ACHBLF patients were followed up for one month. The end of the follow-up was death or survival. The date of diagnosis was the start date of the follow-up.

2.2. Measure plasma DAO level by enzymelinked immunosorbent assay

Five millilitres of fasting venous peripheral blood was collected from each subject, using ethylene diamine tetraacetic acid as anticoagulant agent, six o'clock in the morning of the next day after admission to the hospital, which was then stored at −80 °C after centrifugation. The plasma DAO concentration was measured using the highly sensitive Human diamine oxidase (DAO) ELISA kit (Lengton, shanghai, China), operated according to the instructions. Simply, Add 100 μL of Standard, Blank, or Sample per well. Cover with the Plate sealer. Incubate for 1 h at 37 °C. Remove the liquid of each well, and wash 5 times with Wash Buffer. Add 50 μL Detection Reagent A, and then add 50 μL Detection Reagent B per wel, and then gently shake blending, 37 °C avoid light color for 10 min. Add 50 μL of Stop Solution to each well, Determine the optical density of each well at once, using a microplate reader set to 450 nm. The sensitivity of the DAO ELISA Kit is 0.78 ng/mL.

2.3. Clinical parameters

Clinical parameters included TBIL, INR, PTA, ALT, AST, ALB, Cr, Na,AFP, HBsAg, HBeAg WBCs, HGB and PLTs were collected for each patient. Serum HBV-DNA load was measured by a PCR System, the detection sensitivity is 500 IU/mL. All the serum biochemical markers were measured using standard methodologies in the Department of Laboratory Medicine, Qilu Hospital of Shandong University.

Model for end-stage liver disease (MELD) scores was calculated according to the following formula: MELD score = 3.78× ln (total bilirubin [mg/dL]) + 11.2× ln (INR) + 9.57× ln(creatinine [mg/dL]) + 6.43 [26].
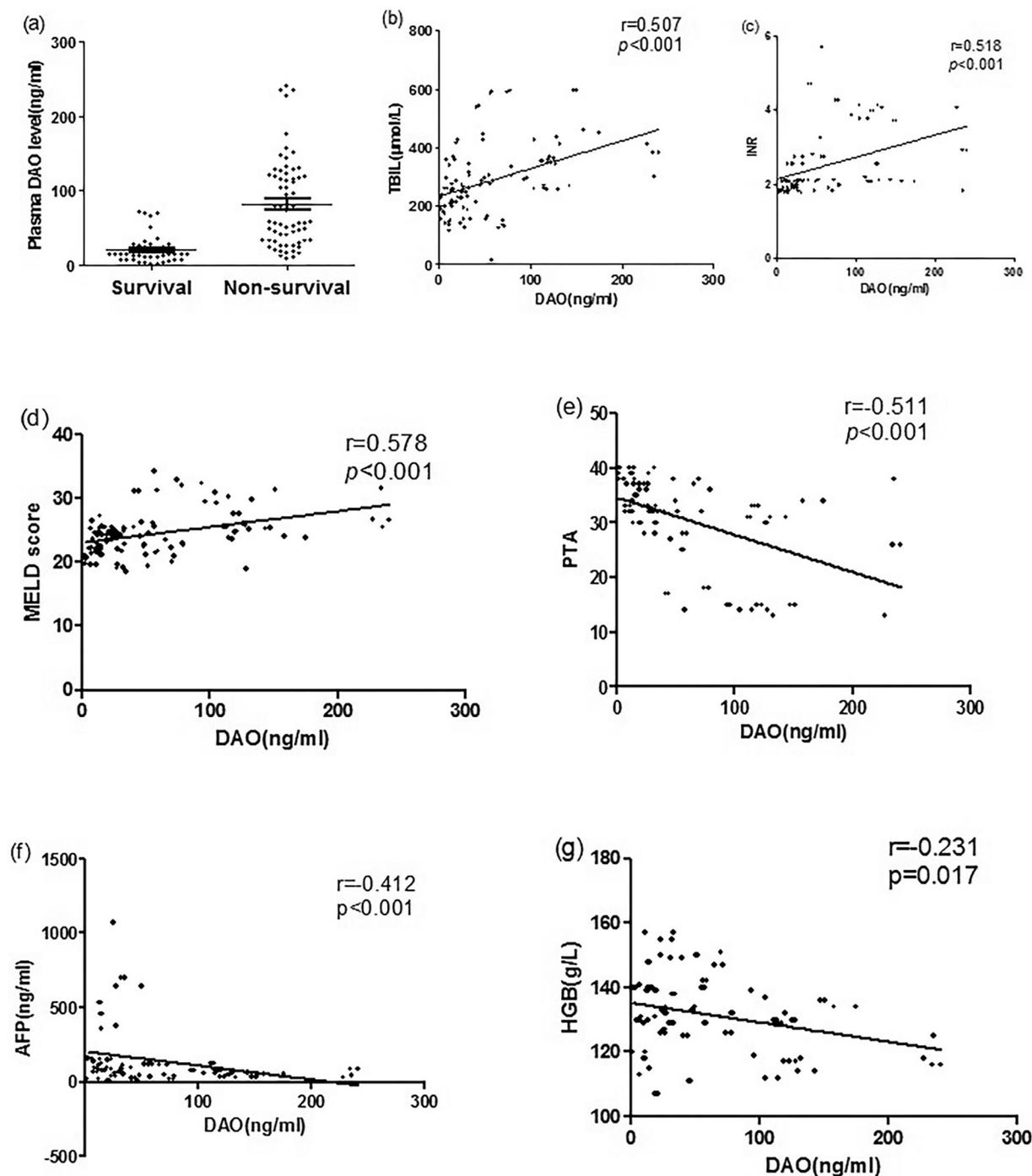
Fig. 2. The plasma DAO levels in survivals and nonsurvivals at the end of 1-month follow up and the associations of plasma DAO level with clinical parameters in ACHBLF patients. The level of DAO in survivals [14.0 (7.1; 26.5) ng/mL] was significantly decrsased than that in nonsurvivals [58.6 (32.5;121.3) ng/mL, $P < .001$] at the end of 1-month follow-up (a), The plasma DAO level was significantly correlated with TBIL ($r = 0.507$, $P < .001$) (b), The plasma DAO level was significantly correlated with INR ($r = 0.518$, $P < .001$) (c), The plasma DAO level was significantly correlated with MELD score ($r = 0.578$, $P < .001$) (d), The plasma DAO level was significantly correlated with PTA ($r = -0.511$, $P < .001$) (e), The plasma DAO level was significantly correlated with AFP ($r = -0.412$, $P < .001$) (f), The plasma DAO level was significantly correlated with HGB ($r = -0.231$, $P = .017$) (g).

2.4. Statistical analysis

Statistical analyses were conducted with the SPSS 19.0 software (SPSS Inc., Chicago, USA) and MedCalc 15.6 software (MedCalc Software, Ostend, Belgium). Categorical values were expressed as relative frequencies (%), and continuous values were expressed as median (centile 25; centile 75). Categorical data was analysed by chi-squared test, and continuous variables was analysed by the Mann–Whitney U test and the Wilcoxon signed rank test. Spearman correlation was used to analyze the relationship between clinical and laboratory parameters with DAO. Univariate logistic analysis were performed to determine the association of clinical and laboratory parameters with prognosis, and then, the forward conditional step-wise logistic analysis was used to identify the independent risk factors for the prognosis of ACHBLF. Receiver operating characteristic (ROC) curve was used to assess the diagnostic value of DAO and DAO plus MELD score. And then

Table 2

Uni- and multivariate logistic analysis of prognosis factors associated with survival in ACHBLF patients.

Variable	Univariate			Mutlivariate		
	OR	95%CI	P	OR	95%Cl	P
male(%)	1.280	0.491–3.335	0.613			
Age(year)	1.022	1.103–1.041	0.322			
HBeAg(+),n(%)	1.072	0.477–2.409	0.866			
HBsAg	1.000	1.000–1.000	0.092			
HBV-DNA(+),n(%)	0.889	0.362–2.181	0.889			
ALT(IU/L)	0.998	0.996–1.000	0.133			
AST(IU/L)	0.998	0.995–1.001	0.268			
ALB(g/L)	0.886	0.800–0.980	0.019	0.917	0.761–1.104	0.362
INR	3.673	1.101–12.246	0.034			
MELD score	1.838	1.423–2.372	0.000	1.680	1.076–2.622	0.022
WBC(109/L)	1.016	0.945–1.092	0.664			
HGB(g/L)	0.967	0.933–1.001	0.059			
PLT(109/L)	0.985	0.974–0.997	0.015	0.980	0.958–1.003	0.091
Na(mmol/L)	1.001	0.979–1.024	0.918			
SBP(n,%)[a]	22.800	5.076–102.407	0.000	15.910	1.070–236.606	0.045
Ascites(n,%)[a]	7.731	2.974–20.097	0.000	1.400	0.126–15.608	0.785
HE(n,%)[a]	9.500	3.303–27.327	0.000	7.678	1.528–38.59	0.013
DAO(ng/mL)	1.055	1.029–1.081	0.000	1.053	1.010–1.098	0.016

OR,odds ratio; CI, confidence interval.

[a] Categorical variables were expressed as n (%).

Kaplan–Meier method was used to compare survival time of different cut-off values. Two-sided $P < .05$ was considered statistically significant.

In order to evaluate the joint predictive value of DAO and MELD scores on 1-month mortality, a new variable based on binary logistic regression equation was established:

$$\text{Variable (plasma DAO plus MELD)} = 0.642 \times \text{MELD} + 0.056 \times \text{DAO} - 16.671$$

3. Results

3.1. General characteristics of the study population

The basic characteristics of patients with ACHBLF have been shown in Table 1. We compared the basic clinical parameters included HBsAg, HBeAg, HBV-DNA, ALT, AST, TBIL, INR, PTA, ALB, MELD score, AFP, WBCs, HGB, PLTs, Cr, presence of ascites, SBP, and HE. We found that the group of nonsurvivals had higher median levels of TBIL [305 (262–385) μmol/L vs. 196 (151–248) μmol/L, $P < .001$], MELD score [27.3 (24.8–32.3) vs. 22.0 (20.7–26.5), $P < .001$], and INR [2.5 (2.1–3.7) vs. 1.9 (1.8–2.1), $P < .01$] and and lower median levels ALB [32.3 (30.0–34.7) g/L vs. 34.2 (31.6–37.4) g/L, $P < .05$], PTA [30 (18–33) vs. 38 (32–39), $P < .05$], AFP [56 (39–88) ng/mL vs. 156 (104–416) ng/mL, $P < .001$], and PLT [129 (100–150) $\times 10^9$/L vs. 132 (111–173) $\times 10^9$/L, $P < .05$] than the survival group. In non-survival group, the incidences of ascites (60.6% vs. 17.5%, $P < .001$), SBP (54.5% vs. 5%, $P < .001$) and HE (57.6% vs. 12.5%, $P < .001$) were higher than survival group. Between survival and nonsurvival group, age, HBV-DNA, HBsAg, HBeAg, ALT, AST, WBCs, HGB, Na and Cr were no significantly differences.

3.2. Plasma DAO level in patients with ACHBLF

We measured the plasma DAO level in patients with ACHBLF and found that the level of DAO in survivals [14.0 (7.1; 26.5) ng/mL] was significantly decrsased than that in nonsurvivals [58.6 (32.5;121.3) ng/mL, $P < .001$] at the end of 1-month follow-up, as shown in Fig. 2a.

### 3.3. The correlation between plasma DAO level and clinical parameters of ACHBLF patients

We demonstrate that the plasma DAO level was significantly correlated with TBIL ($r = 0.507$, $P < .001$), INR ($r = 0.518$, $P < .001$), MELD score ($r = 0.578$, $P < .001$), PTA ($r = -0.511$, $P < .001$), AFP ($r = -0.412$, $P < .001$) and HGB ($r = -0.231$, $P = .017$). However, there was no significant associations between DAO level and age, HBsAg, HBeAg, HBV-DNA, ALT, AST, ALB, Cr, WBCs, and PLTs ($P > .05$), respectively. (Fig. 2b–g).

3.4. Plasma DAO was an independent risk factor for 1-month mortality of ACHBLF

We used univariate and multivariate logistic analysis to identify the potential risk factors for 1-month mortality of ACHBLF, as showed in Table 2. The MELD score (OR = 1.838, $P < .001$), plasma DAO level (OR = 1.055, $P < .001$), INR (OR = 3.673, $P < .05$), ALB (OR = 0.886, $P < .05$), PLT (OR = 0.985, $P < .05$), ascites (OR = 7.731, $P < .001$), SBP (OR = 22.800, $P < .05$) and HE (OR = 9.500, $P < .05$) were significantly correlated with 1-month mortality of ACHBLF. Furthermore, the plasma DAO level (OR = 1.053, $P < .05$), HE (OR = 7.678, $P < .05$), SBP (OR = 15.91, $P < .05$) and MELD score (OR = 1.680, $P < .05$) were independent factors associated with the 1-month mortality for ACHBLF in multiple logistic regression analysis.

3.5. The predictive value of plasma DAO level, MELD score and DAO plus MELD score of 1-month mortality in patients with ACHBLF

The 1-month mortality of ACHBLF was 62.3% (66/106). Nonsurvivals showed significantly higher plasma DAO level [58.6 (32.5;121.3) ng/mL] than that in survivals [14.0 (7.1; 26.5) ng/mL, $P < .001$] as shown in Fig. 2a. The mean survival time of ACHBLF patients was 13.076 (SE 0.851, 95% CI: 14.408–14.744) days. The AUROC for plasma DAO was 0.880 (SE 0.0329, 95% CI 0.803–0.935) and 0.843 (SE 0.0391, 95% CI 0.760–0.907) for MELD score ($P = .43$), and there was no statistical significance between them. Therefore, we further calculated the effect of the DAO plus MELD score for the 1-month mortality of ACHBLF. The AUROC for DAO plus MELD socre was 0.916 (SE 0.0256, 95% CI 0.846–0.961), it was higher than MELD
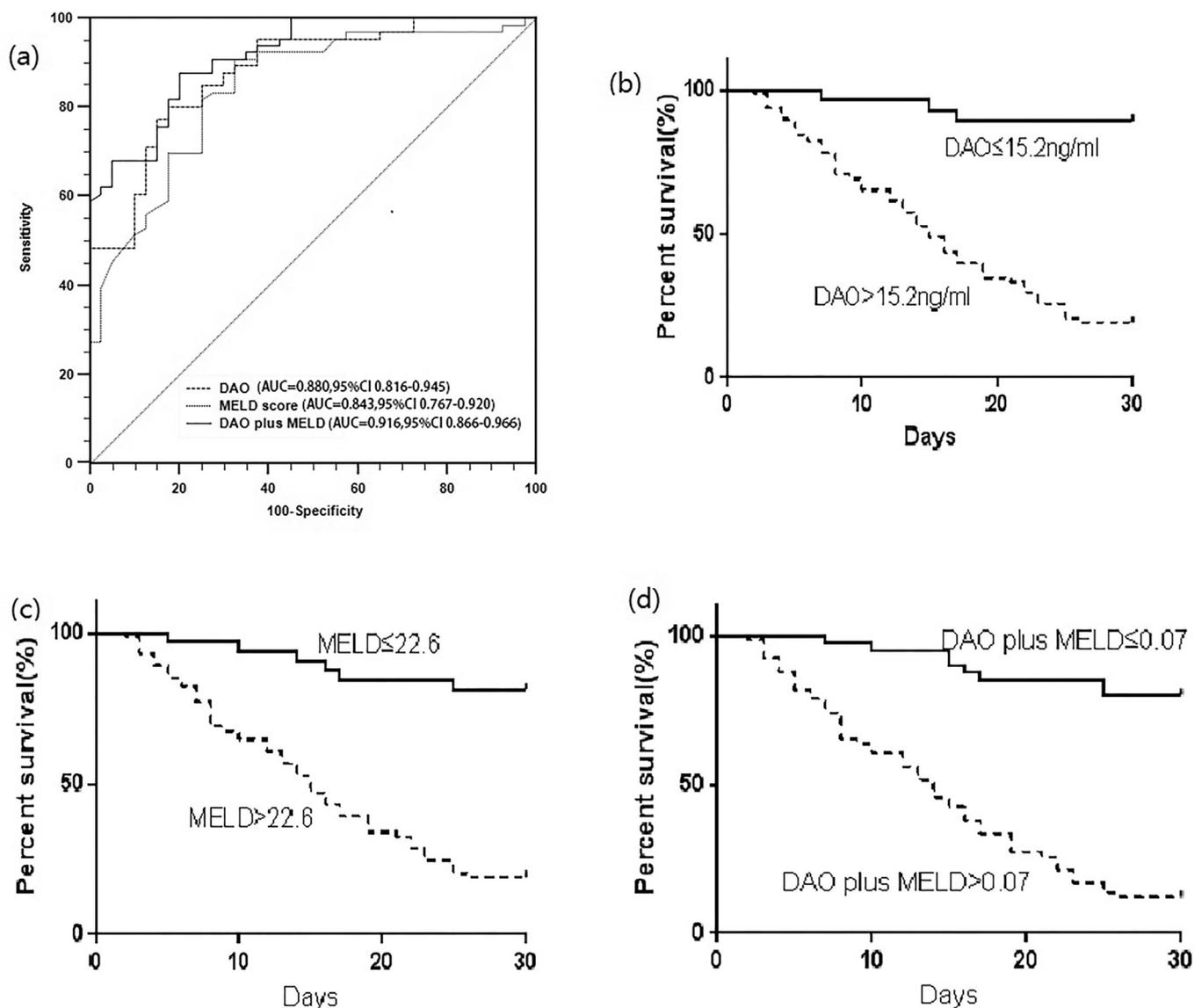
Fig. 3. Sensitivities and specificities for plasma DAO, MELD score and combination of DAO plus MELD score for predicting 1-month mortality of ACHBLF patients (a). Kaplan–Meier survival curves for plasma DAO at the optimal cut-off value 15.2 ng/mL, MELD at 22.6, DAO plus MELD at 0.07 at the end of 1-month follow-up (b, c and d).

significantly ($P < .05$), as shown in Fig. 3a. The cut-off point of 15.2 ng/mL for plasma DAO level with sensitivity of 95.45%, specificity of 62.5%, 22.6 for MELD score with sensitivity of 90.91%, specificity of 67.5%, 0.07 for DAO plus MELD with sensitivity of 87.88%, specificity of 80% were selected to discriminate 1-month morality of ACHBLF. Furthermore, the mean survival time of ACHBLF patients with the level of plasma DAO ≤ 15.2 ng/mL and > 15.2 ng/mL were 28.179 days (SE 1.029, 95% CI: 26.162–30.195) and 16.28 days (SE 1.037, 95% CI: 14.185–18.251; $P < .001$, log-rank test). In addition, the survival rate of patients group with DAO > 15.2 ng/mL was significantly lower than that with DAO ≤ 15.2 ng/mL (Fig. 3b). The mean survival time of ACHBLF patients with MELD ≤ 22.6 and > 22.6 were 27.094 days (SE 1.170, 95% CI: 24.801–29.386) and 16.041 days (SE 1.063, 95% CI: 13.956–18.125; $P < .001$, log-rank test). And the survival rate of patients group with MELD > 22.6 was significantly lower than that with MELD ≤ 22.6 (Fig. 3c). The mean survival time of ACHBLF patients with DAO plus MELD ≤ 0.07 and > 0.07 were 27.250 days (SE 0.965, 95% CI: 25.358–29.142) and 14.606 days (SE 1.055, 95% CI: 12.538–16.674; $P < .001$, log-rank test). And the survival rate of patients group with DAO plus MELD > 0.07 was significantly lower than

that with DAO plus MELD ≤ 0.07 (Fig. 3d). In summary, plasma DAO might be indicating 1-month mortality of ACHBLF patients. Moreover, the DAO plus MELD score could predict the prognosis of ACHBLF better.

4. Discussion

ACHBLF has developed rapidly and has a high short-term mortality. So far, there are many models or markers that used to predict the mortality of patients with ACHBLF [27,28]. In our previous studies, we have confirmed that the gene methylation of glutathione-stransferase p1 and plasma interleukin-10 level can predict ACHBLF mortality [29–31]. However, there was little research on the diagnostic value for intestinal microecological markers for the short-term prognosis of ACHBLF. For the first time in this study, we found that after 1-month follow-up, the plasma DAO level of survivals was lower than those of nonsurvivals significantly. The plasma DAO level was associated with MELD score, TBIL, INR and PTA significantly. In addition, we confirmed that plasma DAO was an independent risk factor for 1-month mortality of ACHBLF. We also confirmed that the DAO plus MELD score could

better predict the prognosis of patients with ACHBLF.

The DAO is a highly concentrated enzyme in the intestinal mucosa of humans and other mammals species, which was confirmed as a pleiotropic circulating biomarker with intestinal mucosal maturation and interity. Furthermore, DAO is the most sensitive indicator for the prediction of intestinal barrier function [32]. In this study, we found that the plasma DAO level was positively correlated with the indicators of the severity of ACHBLF disease, such as TBIL, MELD, and INR. So we speculated that the DAO level could reflect the severity of ACHBLF. Patients with chronic liver disease have shown to have disturbances of the microecology of the indigenous gut flora and small-intestinal bacterial overgrowth (SIBO) [33]. The fecal microbial community in patients with cirrhosis is significantly different from that of healthy people, and there is an imbalance of intestinal microecology, which may further affect the prognosis of patients with cirrhosis [34]. The excessive growth of intestinal bacteria and the decrease of intestinal function can lead to the changes of intestinal permeability, which can increase the chance of infection [35]. Chronic liver diseases and portal hypertension lead to decreased intestinal function, which resulting in excessive growth and displacement of bacteria, thus leading to increased intestinal wall permeability [36]. In animal experiments, it was proved that the small intestinal bacterial overgrowth could further impair intestinal motility, thus forming a vicious cycle and aggravating the development of diseases [37]. Increased intestinal permeability can increase the incidence of hepatic encephalopathy and spontaneous peritonitis, which can increase mortality of ACHBLF.

Previous research found that about 50–90% ACHBLF patients were died within 1-month [3,4]. In this study, 66 ACHBLF patients were dead while 40 survivals at the end of 1 month, the mortality is about 62.3%, which is consistent with previous reports. At present, the most commonly used prognosis model of ACHBLF is the MELD score, which contains the influence of bilirubin, creatinine, coagulation function and etiology. In our prensent study, We showded that MELD and DAO were independent risk factors for the prognosis of ACHBLF. So we combined MELD scores and DAO to analyze the prognosis of patients with ACHBLF and thus compensate for the effect of intestinal microecology on the prognosis of ACHBLF. In previous studies, many indicators were founded could predict ACHBLF the prognosis, for example IL-10 and GSPT1 gene promoter methylation, but this study is the first time to study the relationship between DAO and ACHBLF prognosis as a intestinal microecology biomarker. The mean survival time of ACHBLF patients with the level of plasma DAO ≤ 15.2 ng/mL and > 15.2 ng/mL were 28.179 days and 16.28 days ($P < .001$). In addition, the survival rate of patients group with DAO > 15.2 ng/mL was significantly lower than that with DAO ≤ 15.2 ng/mL. The mean survival time of ACHBLF patients with DAO plus MELD ≤ 0.07 and > 0.07 were 27.250 days and 14.606 days ($P < .001$). And the survival rate of patients group with DAO plus MELD > 0.07 was significantly lower than that with DAO plus MELD ≤ 0.07. The AUROC for DAO plus MELD socre was 0.916, which was higher than MELD significantly ($P < .05$) In summary, plasma DAO might be indicating 1-month mortality of ACHBLF patients. Moreover, the DAO plus MELD score could predict the prognosis of ACHBLF better.

However, there are some limitations in our research. First, we only did a retrospective single-center study without a validation cohort in multiple centers; second, the exact mechanism about how DAO participates in the progress of ACHBLF was still unclear, and further search on this issue is urgent.

In summary, we firstly demonstrated that plasma DAO level was correlated with the severity of ACHBLF. Furthermore, we also demonstrated that the DAO plus MELD > 0.07 predicts poor 1-month mortality of ACHBLF.

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Conflict of interest

None.

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