# Predictive value of elevated serum D-dimer for short-term prognosis in patients with HBV-related acute-on-chronic liver failure

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**Abstract.** To study the predictive value of elevated serum D-dimer on short-term prognosis in patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) and the correlation between serum D-dimer level and the clinical data of these patients, a single center retrospective study was conducted to collect the clinical data and 28 and 90-day survival rates of 201 patients. Logistic regression analysis and receiver operating characteristic curves were used to determine the factors affecting short-term prognosis. A Kaplan-Meier curve was used to compare the difference in survival rate between the two groups with elevated D-dimer and normal D-dimer levels. Correlation analysis was used to determine the correlation between serum D-dimer level and the clinical data of the patients. The results showed that international normalized ratio (INR) >2.3 and age >53 years were independent risk factors affecting the 28-day survival rate of the patients (P<0.05). INR >2.3, serum total bilirubin >358.2 $\mu$mol/l, age >49 years and elevated serum D-dimer (>550 ng/ml) were independent risk factors affecting the 90-day survival rate of the patients (P<0.05). There were significant differences in the 90-day survival rate and the survival time between the patients with elevated D-dimer and normal D-dimer levels (P<0.05). Serum D-dimer level was positively associated with age, combined spontaneous peritonitis, albumin, INR and the model for end-stage liver disease sodium (MELD-Na) scores, and negatively associated with male sex, red blood cell count, and serum sodium and fibrinogen levels. It was concluded that elevated serum D-dimer (>550 ng/ml) is an independent risk factor affecting the 90-day survival rate of patients with HBV-ACLF. The 90-day survival rate and the survival time of patients with HBV-ACLF and elevated D-dimer levels are significantly lower than those with normal D-dimer levels. Overall, serum D-dimer is associated the short-term prognosis of patients with HBV-ACLF, and the detection of serum D-dimer level at admission can help predict the short-term prognosis of patients with HBV-ACLF, especially the 90-day prognosis.

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*Abbreviations:* HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; MELD-Na, model for end-stage liver disease sodium; APASL, Asia-Pacific Association for the Study of Liver; ROC, receiver operating characteristic; SBP, spontaneous peritonitis; INR, international normalized ratio; TBil, total bilirubin; DIC, disseminated intravascular coagulation

*Key words:* ACLF, short-term prognosis, D-dimer, coagulation, fibrinolysis

## Introduction

Acute-on-chronic liver failure (ACLF) refers to acute liver injury that occurs on the basis of underlying liver disease, with jaundice and coagulation disorders as the main manifestations, short-term complications of ascites and hepatic encephalopathy, often combined with multiple organ failure, and high short-term mortality rates (1-3). HBV-ACLF is the most common type of ACLF in China. The international time window for liver failure and ACLF progression has been changed several times, from the initial 12 to 4 weeks, and again back to 12 weeks (4). Data from the large Asia-Pacific Association for the Study of Liver (APASL)-ACLF Research Consortium database showed that ~70% of patients surviving >90 days exhibited a reversal of ACLF syndrome, showing sustained regression of the disease after 1 year. Therefore, the 90-day survival rate of patients with ACLF not only reflects their short-term prognosis, but also has great implications for their long-term prognosis (1). The disease progresses rapidly in patients with ACLF, and liver failure or extrahepatic organ failure caused by acute events can occur rapidly, with a dangerous prognosis (5). Therefore, the early and correct diagnosis of ACLF and the determination of indicators related to the poor prognosis of the disease are crucial for the prognosis prediction and treatment of patients (6).

The reconstituted hemostasis pattern in the disturbed internal environment of patients with ACLF is a subtle

balanced hemostasis characterized by the coexistence of hypocoagulability and hypercoagulation, which may lead to the occurrence of hemorrhagic or prothrombotic states (7-9). In the progression of ACLF, subsequent organ failure may further exacerbate the hemostatic imbalance caused by cirrhosis (10,11). Secondary fibrinolysis due to intrahepatic hypercoagulability may be related to elevated serum D-dimer levels in patients with ACLF (12). D-dimer, a marker of activation of the coagulation and fibrinolytic systems, and an indirect marker of thrombotic activity (13), is elevated in critically ill patients with cirrhosis (14). The level of serum D-dimer of patients with liver cirrhosis gradually increases with the aggravation of liver dysfunction (15,16). Higher D-dimer levels can significantly predict in-hospital mortality in patients with cirrhosis; therefore, D-dimer detection can be used for prognostic stratification in cirrhosis (17,18). The association of D-dimer with multiple organ injury confirms its association with systemic inflammatory responses, thus, as well as being a marker of fibrinolytic activation, D-dimer is also a sign of severe systemic inflammation (12). A retrospective study by Qi *et al* (12) showed that D-dimer levels were related to the 28-day mortality rate of patients with ACLF, and the risk of 28-day mortality in patients with ACLF increased when the level of D-dimer reached 6.5 mg/l FEU. The research conclusions need to be further confirmed.

## Materials and methods

*Study design*. A single center retrospective study was conducted to screen patients who were hospitalized in The Second Affiliated Hospital of Chongqing Medical University (Chongqing, China) between August 2017 and May 2021. The inclusion criteria included: i) met the diagnostic criteria of APASL ACLF; ii) a diagnosis of ACLF combined with HBV infection; and iii) age within 12-80 years old. The exclusion criteria included: i) a diagnosis of ACLF combined with deep vein thrombosis or portal vein thrombosis; ii) a diagnosis of ACLF combined with liver cancer or other malignant tumors; iii) a diagnosis of ACLF combined with severe chronic extrahepatic diseases; iv) a diagnosis of ACLF combined with atrial fibrillation, coronary heart disease or acute aortic dissection; v) a diagnosis of ACLF combined with human immunodeficiency virus infection; vi) major surgery or trauma within the last 6 months; vii) received anticoagulation therapy within the past month; viii) received immunosuppressive therapy; and ix) pregnant women. A total of 201 patients with HBV-ACLF were included. All patients received standardized medical treatment [according to the Diagnostic and Treatment Guideline for Liver Failure 2018 (19)] and artificial liver support system treatment during hospitalization, and none of the patients received liver transplantation.

*Data collection*. Patient data, including age, sex, comorbidities, laboratory test results and prognostic scores, were collected via electronic medical records, and 28 and 90-day survival rates were collated using electronic medical record review and/or standardized telephone interviews. Serum D-dimer level was detected as part of the initial patient tests during the hospitalization period and it was detected by the immunofluorescence method. This method is based on immunofluorescence technology and adopts the double-antibody sandwich method. The sample to be tested is mixed with the detection buffer, and the immunolabeled detection antibody in the buffer will bind to the D-dimer antigen. The intensity of the fluorescent antibody signal is proportional to the concentration of the captured D-dimer, and the concentration of the antigen in the sample can be calculated after being analyzed by an immunoassay analyzer. The type of the analyzer was Jet-iStar3000 produced by Joinstar company, and the D-dimer detection kit produced by Joinstar company was used. The analyzer and kit was used to test the serum samples from 160 healthy individuals and the normal reference range of D-dimer was confirmed to be <550 ng/ml. According to whether the serum D-dimer level was increased (>550 ng/ml), the patients were divided into the elevated D-dimer group and the normal D-dimer group.

*Statistical analysis*. Continuous variables with normal distribution were expressed as the mean ± standard deviation, non-normally distributed continuous variables were expressed as the median (inter-quartile range) and nominal variables were expressed as n (%). The influencing factors of 28 and 90-day prognosis were determined by univariate and multivariate logistic regression analysis, and the sensitivity and specificity of influencing factors were determined by receiver operating characteristic (ROC) curves. Among the influencing factors, the binary variable was determined by the $\chi^2$ test, and its specificity and sensitivity were calculated. Pearson's correlation analysis was performed between the serum D-dimer levels and various baseline data (the point biserial correlation coefficient of continuous variables and dichotomous variables was consistent with the values of Pearson's correlation coefficient). A Kaplan-Meier curve was drawn, and Breslow's test was used to compare the difference in survival between the two groups. All statistical analyses were performed using SPSS v.26.0 (IBM Corp.) and all figures were drawn with GraphPad Prism 9.0 (GraphPad Software, Inc.). $P<0.05$ was used to indicate a statistically significant difference.

## Results

*Baseline data*. Of the 201 patients, 18 were lost to follow-up. Among the 183 patients, 162 were male and 21 were female, with a mean age of 47.9 years. Overall, 71.6% of patients had underlying cirrhosis, 53.0% had spontaneous peritonitis (SBP) and 61.7% had an elevated serum D-dimer level at baseline (Table I).

*Logistic analysis and ROC curve*. Multivariate logistic analysis was performed on the patient's baseline data and the 28 and 90-day prognosis of the patients, and the independent risk factors affecting the 28 and 90-day survival rates were obtained. ROC curve was used to analyze the predictive value of these factors on 28 and 90-day survival. The critical value of each indicator was calculated using Jordan index (20).

The results showed that international normalized ratio (INR) >2.3 and age >53 years were independent risk factors affecting 28-day survival ($P<0.05$) (Figs. 1 and 2; Table II). INR >2.3, serum total bilirubin (TBil) >358.2 $\mu$mol/l, age >49 years and elevated serum D-dimer (>550 ng/ml) were independent risk factors affecting 90-day survival ($P<0.05$) (Figs. 3 and 4; Tables III and IV).

Table I. Baseline data of patients (n=183).

| Variable | Value | Normal range |
|---|---|---|
| Age, years | 47.9±11.3 | |
| Male sex | 162 (88.5%) | |
| Cirrhosis | 131 (71.6%) | |
| SBP | 97 (53.0%) | |
| Red blood cell count (x$10^{12}$/l) | 4.1±0.7 | 4.3-5.8 |
| Hemoglobin, g/l | 131.9±20.8 | 130-175 |
| Leucocyte count (x$10^{9}$/l) | 6.4 (4.9-8.6) | 3.5-9.5 |
| Neutrophil percentage | 72.0 (66.8-80.7) | 45-75% |
| Platelet count (x$10^{9}$/l) | 94 (68.0-125.0) | 100-300 |
| Alanine aminotransferase, U/l | 578 (193.0-1,222.0) | 9-50 |
| Aspartate aminotransferase, U/l | 385 (150.0-931.0) | 15-40 |
| Serum total bilirubin, $\mu$mol/l | 298.3 (236.7-373.7) | 5.1-28 |
| Albumin, g/l | 31.1±4.1 | 40-55 |
| Serum creatinine, $\mu$mol/l | 57.7 (49.5-71.0) | 57-97 |
| Serum sodium, mmol/l | 134.9±4.0 | 137-147 |
| INR | 2.2 (1.9-2.9) | 0.7-1.3 |
| Fibrinogen, g/l | 1.5 (1.2-1.9) | 2-4 |
| MELD-Na score | 24.8 (21.0-28.8) | |
| $Log_{10}$HBV-DNA | 5.0 (3.8-6.7) | |
| Serum D-dimer, ng/ml | 902 (345.2-1,634.6) | 0-550 |
| Elevated D-dimer group | 113 (61.7%) | |
| 28-day mortality | 50 (27.3%) | |
| 90-day mortality | 89 (48.6%) | |

Continuous variables with normally distribution are expressed as the mean ± standard deviation, non-normally distributed continuous variables are expressed as the median values (inter-quartile range) and nominal variables are expressed as n (%). INR, international normalized ratio; SBP, spontaneous peritonitis; HBV, hepatitis B virus; MELD-Na, the model for end-stage liver disease sodium.

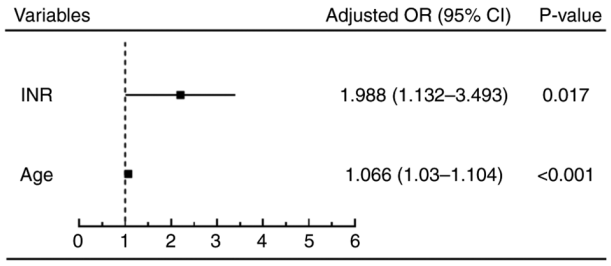


Figure 1. Forest plot of 28-day prognostic factors. INR, international normalized ratio.

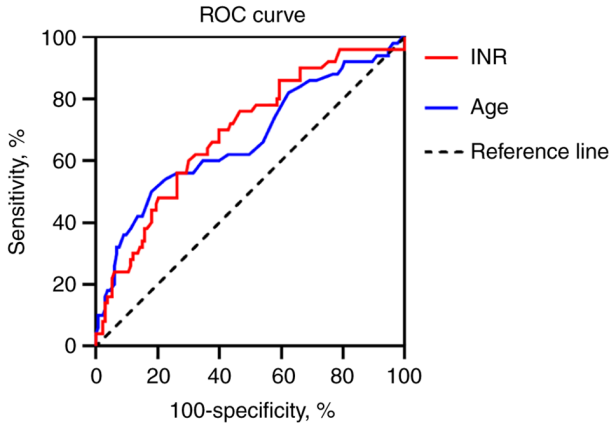


Figure 2. ROC curve of 28-day prognostic factors. ROC, receiver operating characteristic; INR, international normalized ratio.

*Survival analysis*. After 90 days of follow-up, 18 of the 201 patients were censored. A Kaplan-Meier curve was drawn, and the Breslow test was used to compare the difference in survival between the elevated D-dimer and normal D-dimer groups. The results showed that there were significant differences in the 90-day survival rate and the survival time between the two groups (P<0.05). The 90-day survival rate and the survival time of patients in the elevated D-dimer group were significantly lower than those in the normal D-dimer group (Fig. 5).

*Correlation analysis*. Pearson's correlation analysis was performed between the serum D-dimer levels and various baseline data (the point biserial correlation coefficient of continuous variables and dichotomous variables was consistent with the values of Pearson's correlation coefficient). The results showed that serum D-dimer level was negatively associated with male sex (r=-0.146, P=0.049), red blood cell count (r=-0.173, P=0.019), serum sodium (r=-0.158, P=0.033) and fibrinogen (r=-0.273, P<0.001), and positively associated with

Table II. Receiver operating characteristic curve analysis of 28-day prognostic factors.

| Factor | AUC | 95% Confidence interval | P-value | Specificity, % | Sensitivity, % | Associated criterion |
|---|---|---|---|---|---|---|
| INR | 0.688 | 0.616-0.754 | <0.0001 | 60.15 | 70.00 | >2.3 |
| Age | 0.668 | 0.595-0.736 | 0.0005 | 81.95 | 50.00 | >53 years |

INR, international normalized ratio; AUC, area under the curve.

Table III. Receiver operating characteristic curve analysis of 90-day prognostic factors.

| Factor | AUC | 95% Confidence interval | P-value | Specificity, % | Sensitivity, % | Associated criterion |
|---|---|---|---|---|---|---|
| INR | 0.696 | 0.624-0.762 | <0.0001 | 68.09 | 65.17 | >2.3 |
| TBil | 0.656 | 0.582-0.724 | 0.0001 | 82.98 | 43.82 | >358.2 $\mu$mol/l |
| Age | 0.655 | 0.581-0.724 | 0.0001 | 70.21 | 53.93 | >49 years |

INR, international normalized ratio; TBil, total bilirubin; AUC, area under the curve.

Table IV. $\chi^2$ test of elevated serum D-dimer and 90-day survival.

| | 90-Day survival, n (%) | | | | | |
|---|---|---|---|---|---|---|
| Patient group | Died | Survived | $\chi^2$ | P-value | Specificity, % | Sensitivity, % |
| Elevated D-dimer | 66 (36.07) | 47 (25.68) | 11.295 | 0.001 | 50.00 | 74.16 |
| Normal D-dimer | 23 (12.57) | 47 (25.68) | | | | |

Elevated serum D-dimer as a binary variable is not suitable for ROC curve analysis, thus, a $\chi^2$ test was performed for elevated serum D-dimer and 90-day survival, and its specificity and sensitivity were calculated.

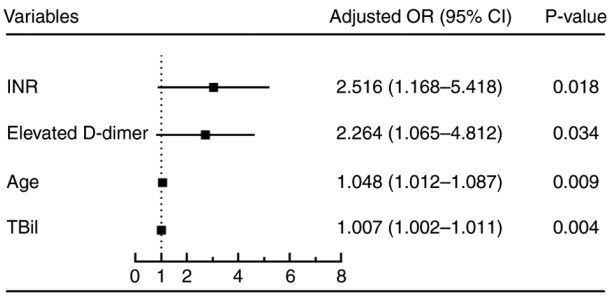


Figure 3. Forest plot of 90-day prognostic factors. INR, international normalized ratio; TBil, total bilirubin.

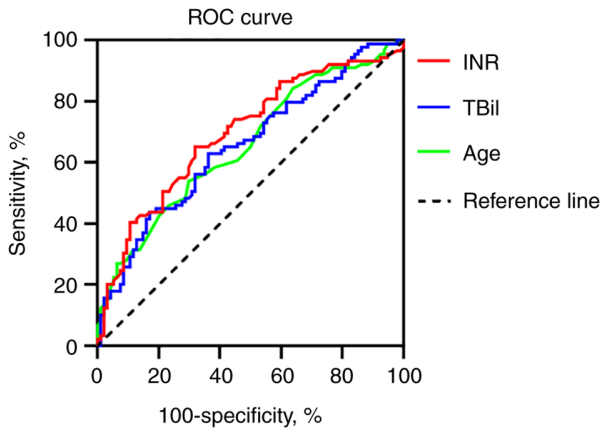


Figure 4. ROC curve of 90-day prognostic factors. ROC, receiver operating characteristic; INR, international normalized ratio; TBil, total bilirubin.

age (r=0.155, P=0.037), combined SBP (r=0.149, P=0.044), albumin (r=0.160, P=0.031), INR (r=0.149, P=0.044) and MELD-Na score (r=0.174, P=0.018) (Table V).

## Discussion

D-dimer is a sensitive marker of coagulation and fibrinolysis, and studies have found that serum D-dimer is elevated in liver failure and portal vein thrombosis (21). In the mouse model of acute liver failure, both hepatic hypercoagulability and fibrin deposition are present (13,14,22). The results of the present study showed that the level of serum D-dimer was significantly negatively associated with fibrinogen (r=-0.273), which reflected the presence of hypercoagulable states in the patients with ACLF. It has been found that SBP may play an active role in the pathogenesis of accelerated plasma fibrinolysis in patients with liver cirrhosis (23). The present study showed that plasma D-dimer levels were significantly

Table V. Correlation analysis of serum D-dimer with baseline data.

| Variable | Correlation coefficient (r) | P-value |
|---|---|---|
| Age, years | 0.155 | 0.037 |
| Male sex | -0.146 | 0.049 |
| Cirrhosis | 0.030 | 0.688 |
| SBP | 0.149 | 0.044 |
| Red blood cell count ($x10^{12}$/l) | -0.173 | 0.019 |
| Hemoglobin, g/l | -0.119 | 0.109 |
| Leucocyte count ($x10^9$/l) | 0.050 | 0.501 |
| Neutrophil percentage | 0.040 | 0.586 |
| Platelet count ($x10^9$/l) | 0.047 | 0.527 |
| Alanine aminotransferase, U/l | -0.126 | 0.090 |
| Aspartate aminotransferase, U/l | -0.013 | 0.857 |
| Serum total bilirubin, $\mu$mol/l | 0.064 | 0.389 |
| Albumin, g/l | 0.160 | 0.031 |
| Serum creatinine, $\mu$mol/l | -0.081 | 0.278 |
| Serum sodium, mmol/l | -0.158 | 0.033 |
| INR | 0.149 | 0.044 |
| Fibrinogen, g/l | -0.273 | <0.001 |
| MELD-Na score | 0.174 | 0.018 |
| $Log_{10}$HBV-DNA | -0.040 | 0.587 |

INR, international normalized ratio; SBP, spontaneous peritonitis; HBV, hepatitis B virus; MELD-Na, the model for end-stage liver disease sodium.

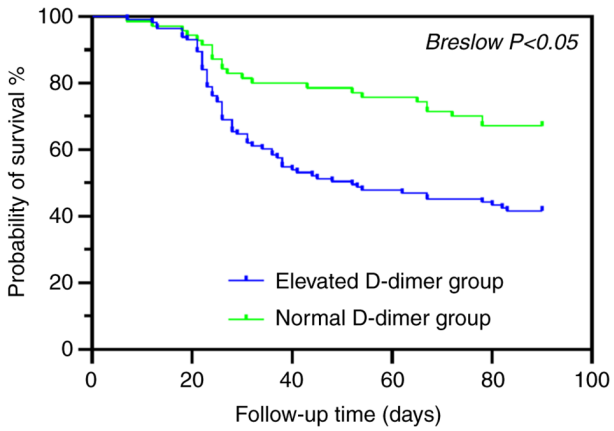


Figure 5. Kaplan-Meier survival curve of the elevated D-dimer and normal D-dimer groups.

positively associated with combined SBP (r=0.149). Thus, it can be inferred that secondary fibrinolysis caused by intrahepatic hypercoagulability may be associated with the elevation of serum D-dimer in patients with ACLF, and the presence of SBP may play a certain role in promoting this process. In addition, a study reports that a significant increase in baseline serum von Willebrand factor (vWF) level in patients with ACLF is associated with a marked reduction in survival time, which may be due to vWF further promoting the formation of a hypercoagulable state in patients with ACLF (24). The significance of both coagulation and fibrinolysis in ACLF progression was underscored in these findings.

Infection and sepsis are common in patients with ACLF, and their presence or development is associated with poor outcomes (25,26). Sepsis is usually associated with infections such as SBP, pulmonary infections and urinary tract infections (27). A study by El Gohary *et al* (23) confirmed that the level of serum D-dimer in patients with SBP was significantly higher than that in normal subjects and those without SBP, and serum D-dimer was efficient in the early diagnosis of SBP in patients with liver cirrhosis. The results of the present study also showed that the serum D-dimer level was significantly positively associated with SBP (r=0.149). Therefore, it can be considered that the increase in serum D-dimer level can reflect whether patients with ACLF have SBP complications to a certain extent.

Microvascular thrombosis is associated with the activation of the coagulation system and inflammation, which causes multiple organ failure in patients with sepsis (28). It has also been found that acute inflammatory responses in patients with ACLF may trigger endothelial activation, resulting in markedly elevated vWF levels, leading to progressive occlusion of small vessels and secondary thrombotic microangiopathy, which is associated with multiorgan failure and short-term mortality (29). It has also been found that hemostatic changes in patients with ACLF partially overlap with those of patients with sepsis-related disseminated intravascular coagulation (DIC). Therefore, interventions that improve the prognosis of sepsis-related DIC may also be beneficial for patients with ACLF (30).

The study by El Gohary *et al* (23) found that the serum D-dimer concentration increased with the deterioration of liver function, and that the serum D-dimer level increased significantly with the severity of liver disease. The clinical indicators used to evaluate liver function mainly include TBil, INR and albumin. The results of the present study showed that serum D-dimer level was significantly positively associated with INR (r=0.149), which was an independent risk factor affecting both the 28 and 90-day survival of the patients. Serum D-dimer level was significantly positively associated with albumin (r=0.160), but there was no significant association between serum D-dimer level and TBil (P=0.389), although TBil was an independent risk factor affecting the 90-day survival of patients, which may be due to the limited sample size.

The limitations of the present study are, first, that all patients included were diagnosed with HBV-ACLF, so the predictive value of serum D-dimer for short-term prognosis in patients with ACLF due to other etiologies remains to be determined. Second, ACLF progresses rapidly, but due to the limitation of retrospective studies, the changes in serum D-dimer levels in the patients with HBV-ACLF could not be dynamically monitored. Whether the short-term increase of serum D-dimer levels has predictive value for the short-term prognosis of HBV-ACLF still needs further research to confirm.

In conclusion, elevated serum D-dimer (>550 ng/ml) was an independent risk factor affecting the 90-day survival rate of the patients with HBV-ACLF (P<0.05). The 90-day survival rate and the survival time of the patients in the elevated D-dimer

group were significantly lower compared with those in the normal D-dimer group (P<0.05). Serum D-dimer is associated with the short-term prognosis of patients with HBV-ACLF, and the detection of serum D-dimer at admission can help predict the short-term prognosis of these patients, especially the 90-day prognosis.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

QC and ZM confirm the authenticity of all the raw data. QC is responsible for data collection, data analysis and writing the paper. ZM and QC designed and performed the study together. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China (approval no. 2022032).

**Patient consent for publication**

All patients in this study provided oral consent for the publication of their data.

**Competing interests**

The authors declare that they have no competing interests.

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