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Research article

LiveBoost: A GB-based prediction system for liver fibrosis in chronic hepatitis B patients in China - A multi-center retrospective study

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ABSTRACT

Background: The aim of this study was to evaluate the accuracy of LiveBoost™, a gradient boosting (GB)-based prediction system based on standard biochemical values (AST, ALT, platelet count) and age, in Chinese patients with chronic hepatitis B (CHB) and compare its performance with FIB-4 (fibrosis-4 score) and APRI (the aspartate transaminase to platelet ratio index).
Methods: This retrospective trial enrolled 454 participants, including 279 CHB patients who underwent liver biopsy and 175 normal controls from 3 centers in China. All participants underwent laboratory blood testing. LiveBoost was constructed using GB and FIB-4 and APRI were calculated from laboratory data.
Results: LiveBoost outperformed APRI and FIB-4 in predicting hepatic fibrosis and cirrhosis. The GB model had an AUROC of 0.977 for CHB diagnosis, 0.804 for early and advanced fibrosis, and 0.836 for non-cirrhosis and cirrhosis, compared to AUROC of 0.554, 0.673 and 0.720 for FIB-4, AUROC of 0.977, 0.652 and 0.654 for APRI.
Conclusions: LiveBoost is a more reliable and cost-effective method than APRI and FIB-4 for assessing liver fibrosis in Chinese patients with CHB.

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1. Introduction

Hepatic fibrosis is a response to various chronic hepatitis diseases, such as chronic hepatitis B (CHB), fatty liver disease, and alcohol consumption [1]. HBV infection affects over 292 million people globally [2]. CHB patients may develop advanced liver fibrosis and progress to cirrhosis, hepatocellular carcinoma or death [3]. Early detection and staging of liver fibrosis is crucial to change the outcome.

Liver biopsy is currently the gold standard for diagnosing liver fibrosis or cirrhosis [4], but it is invasive and has significant complications and sampling error [5,6]. Non-invasive markers have been proposed for diagnosing liver fibrosis [7]. FibroScan is recommended by WHO and other guidelines for evaluating liver fibrosis [8,9], but it is limited by ascites, obesity, and rib gap width [10,11]. WHO and Consensus on hepatic fibrosis (2019) recommend FIB-4 and APRI indices for diagnosis, reducing the need for liver biopsy by 30–40 % [12–15]. Although the diagnostic value of these indices has been widely studied, their sensitivity and specificity remain controversial [16–18]. Hence, novel non-invasive biomarkers or approaches are needed as current biochemical markers do not have enough diagnostic accuracy to replace liver biopsy.

Medical AI technology has significant impact on clinical big data analysis and disease diagnosis, staging, and prognosis [19,20]. We previously used a supervised learning method, gradient boosting (GB) to construct a GB-based prediction system, LiveBoost, for evaluating liver fibrosis grade, and our data showed its potential accuracy and application in liver fibrosis diagnosis [20]. Further validation and comparison in chronic liver disease populations are needed.

In this study, we evaluate the accuracy of LiveBoost in measuring liver fibrosis in CHB patients, comparing its performance to FIB-4 and APRI for staging liver fibrosis using liver biopsy as reference standard.

2. Patients and methods

2.1. Study Design and participants

This retrospective, cross-sectional, multi-center study was conducted at Guangdong Provincial Hospital of Chinese Medicine, Second Hospital of Anhui Medical University, and Beijing Youan Hospital in China. 467 adults were invited to participate from October 2020 to August 2021, with 458 meeting the inclusion criteria and agreeing to participate. Participants were excluded if they were under 18 or over 75, had a history of heavy alcohol consumption in the past 5 years or within 2 weeks, had severe cardiovascular, pulmonary, renal, endocrine, or hematopoietic system diseases, or were pregnant or breastfeeding. The final sample consisted of 454 participants, 279 with chronic hepatitis B and 175 healthy controls. Liver fibrosis or cirrhosis was diagnosed using the Consensus on the diagnosis and treatment of hepatic fibrosis (2019 edition) [15]. Normal controls underwent routine biochemical tests, B-ultrasound, and FibroScan to confirm they were free of inflammation and metabolic diseases. The study was approved by the ethics committees of the three participating hospitals: Guangdong Provincial Hospital of Chinese Medicine (approval no. DF2019-230-02), Second Hospital of Anhui Medical University (approval no. PJ-QX2020-002), and Beijing Youan Hospital (approval no. LL-2020-081-S). All participants provided informed consent to participate in the study.

2.2. Laboratory analysis and estimation of the APRI and FIB-4

Information of CHB patients who underwent liver biopsy in hospitals were reviewed. Clinical and laboratory data were collected for each participant by accessing to their medical records. The series of liver biochemistry parameters were studied: AST, ALT, and platelet count (PLT). Only laboratory tests performed within 14 days after receiving a liver biopsy directed by ultrasonography were included in this study. The FIB-4 [21] and APRI [22] were calculated with the following formulas (1) and (2):

$$\mathrm{FIB}-4=\frac{Age\ (years)\times AST\ (U/L)}{Platelet\ Count\ \left(10^9/L\right)\times\sqrt{ALT\ (U/L)}} \tag{1}$$

$$\mathrm{APRI}=\frac{AST\ (U/L)/\ AST\ (Upper\ Limit\ of\ Normal)\ (U/L)}{Platelet\ Count\ \left(10^9/L\right)}\times 100 \tag{2}$$

2.3. Histological analysis

All patients had a liver biopsy and histological features were analyzed using the Scheuer's scoring system. Fibrosis was staged on a scale of S0 to S4, as follows.

- S0 = no fibrosis.
- S1 = portal fibrosis without septa.
- S2 = few septa.
- S3 = numerous septa without cirrhosis.
- S4 = cirrhosis.

The severity and progression of liver fibrosis is important for treatment decisions, duration, and follow-up strategy, the test should

be able to differentiate liver fibrosis patients from normal controls, to differentiate cirrhosis patients from fibrosis patients, and to differentiate the maximum number of cirrhotic (S4) and advanced fibrosis (S3) from early staged (S1 and S2) fibrotic patients.

2.4. The GB-based prediction system, LiveBoost

The GB-based scoring system, LiveBoost, has received a registration certificate from the National Medical Products Administration of China (Approval No. 20212211795). It uses four factors: age, AST, ALT, and PLT. Further details can be found in our previous study and datasets and R-code related to the model construction can be found at https://github.com/elise-is/LiveBoost [20]. The types of machines and OS was shown in Supplementary table S1. Table S2 shows the versions of the tools used in this study.

2.5. Statistical analysis

Datasets used in this study were provided as Supplementary table S3. Data were analyzed using SAS 9.4. Continuous variables were described as median (IQR) and categorical variables as count/percent.

Diagnostic accuracy measured by AUROC to determine GB-based system's effectiveness in differentiating CHB from control group. Compared performance of FIB-4, APRI with GB-model for differentiation of CHB vs normal control, early liver fibrosis vs advanced

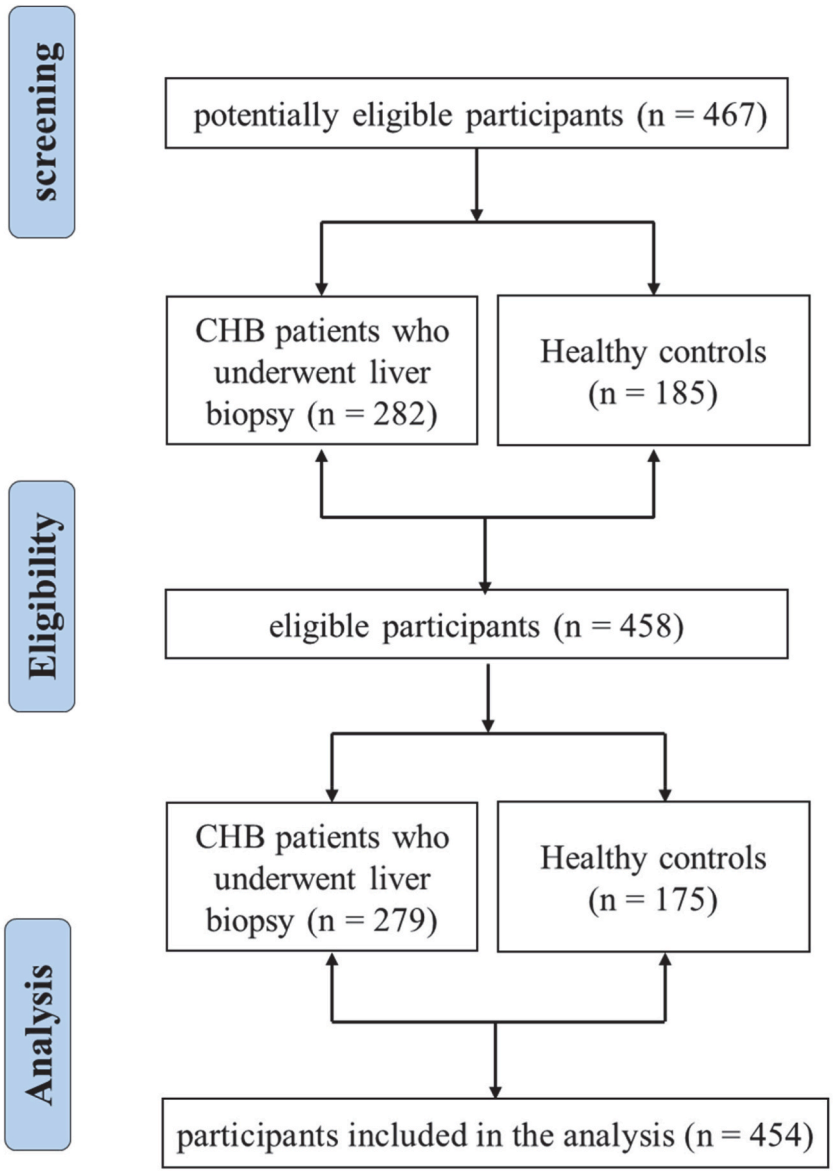

Fig. 1. Flow chart for study participants selection.

fibrosis, and fibrosis vs cirrhosis. Best GB cutoff point selected using Youden's index, while APRI and FIB-4 used previously reported clinical cutoffs [23,24].

Sensitivity, specificity, PPV, NPV along with 95 % CIs calculated at these cutoffs. The confidence interval was calculated using the Wilson score method. McNemar-Bowker test and Fleiss kappa analysis also conducted to compare the result obtained with LiveBoost to the fibrosis degree diagnosed by liver biopsy, evaluating intra- and inter-diagnosis agreements. Significance defined as $P < 0.05$.

3. Results

3.1. Baseline characteristics of participants

Four hundred fifty-four individuals participated in this study, 279 with CHB and liver biopsy, and 175 normal controls without liver biopsy. Fig. 1 shows the enrollment and eligibility of patients. The liver biopsy group consisted of 68.82 % males, with an average age of 35 years (range 28–44). The normal control group (59.43 % males) had an average age of 51 years (range 39–62). Results showed a higher presence of early and advanced fibrosis in CHB group based on liver biopsy or doctor diagnosis (65.59 % vs 0.00 %, 34.41 % vs 0.00 %) and GB-based prediction model (63.80 % vs 0.00 %, 36.20 % vs 4.57 %) (Table 1).

3.2. Differentiating liver fibrosis patients from NC

The GB-based prediction system, using AST, ALT, PLT and age as inputs, showed superior diagnostic accuracy for differentiating liver fibrosis patients from NC with an AUROC of 0.977. Compared to the FIB-4 model, which had an AUROC of 0.554, the GB-based prediction system had excellent results with 100 % sensitivity, 95.4 % specificity, 97.2 % PPV, 100 % NPV, and 98.2 % accuracy ($P < 0.001$ for Bowker, Kappa = 0.962, Tables 2 and 3, Fig. 2A and 3). In the three study sites, GB-based prediction system outperformed APRI and FIB-4 indexes, with AUROC >0.900, sensitivity, specificity, and accuracy >85 % ($P < 0.001$ for Bowker, Kappa >0.900).

3.3. Differentiating advanced fibrosis vs early fibrosis in CHB patients

In this study, early fibrosis was defined as stages 1–2, and advanced fibrosis as stages 3–4. Table 2 shows the accuracy of the GB-based prediction system, APRI, and FIB-4 in differentiating advanced fibrosis from early fibrosis. The GB-based prediction system had better accuracy than APRI and FIB-4. GB-based prediction system had the highest AUROC of 0.804 (Fig. 2B), with a sensitivity of 76.0 %, specificity of 84.7 %, positive predictive value of 72.3 %, negative predictive value of 87.1 %, and accuracy of 81.7 % ($P < 0.001$ for

Table 1
Demographic characteristics and diagnosis results of participants.

Characteristic	Total (N = 454)	Liver biopsy group (N = 279)	Normal control group (N = 175)
Age (years)	39.00 (31.00, 53.00)	35.00 (28.00, 44.00)	51.00 (39.00, 62.00)
Sex, N (%)			
Male	296 (65.20)	192 (68.82)	104 (59.43)
Female	158 (34.80)	87 (31.18)	71 (40.57)
Disease, N (%)			
Yes	154 (33.92)	86 (30.82)	68 (38.86)
No	300 (66.08)	193 (69.18)	107 (61.14)
PLT, N (%)			
Normal	417 (91.85)	245 (87.81)	172 (98.29)
Abnormal	37 (8.15)	34 (12.19)	3 (1.71)
AST, N (%)			
Normal	216 (47.58)	53 (19.00)	163 (93.14)
Abnormal	238 (52.42)	226 (81.00)	12 (6.86)
ALT, N (%)			
Normal	193 (42.51)	27 (9.68)	166 (94.86)
Abnormal	261 (57.49)	252 (90.32)	9 (5.14)
Liver biopsy stage, N (%)			
S1	105 (23.13)	105 (37.63)	–
S2	78 (17.18)	78 (27.96)	–
S3	77 (16.96)	77 (27.60)	–
S4	19 (4.19)	19 (6.81)	–
Diagnosis of doctors, N (%)			
Non-Liver fibrosis	175 (38.55)	–	175 (100)
S1–S2	183 (40.31)	183 (6.56)	–
S3–S4	96 (21.15)	96 (34.41)	–
GB-based prediction model (LiveBoost), N (%)			
Low Liver fibrosis risk	167 (36.78)	–	167 (95.43)
Early Liver fibrosis risk	178 (39.21)	178 (63.80)	–
Advanced Liver fibrosis risk	109 (24.01)	101 (36.20)	8 (4.57)

Continuous variables are displayed as median value (25 %–75 % quantile values).
PLT: platelets; AST, aspartate aminotransferase; ALT: alanine aminotransferase; GB: gradient boosting.

Table 2
Diagnostic accuracy of GB-based system (LiveBoost), FIB-4 and APRI in predicting liver fibrosis and cirrhosis.

	Fibrosis	Advanced Fibrosis	Cirrhosis
FIB-4			
AUROC	0.554	0.673	0.720
Sensitivity (%)		59.0 (cutoff: 1.45)[a]	
		17.7 (cutoff: 3.25)[a]	
Specificity (%)		67.2 (cutoff: 1.45)[a]	
		96.0 (cutoff: 3.25)[a]	
APRI			
AUROC	0.977	0.652	0.654
Sensitivity (%)			63.8 (cutoff: 1.0)[b]
			15.8 (cutoff: 2.0)[b]
Specificity (%)			64.0 (cutoff: 1.0)[b]
			85.0 (cutoff: 2.0)[b]
GB-based system			
AUROC	0.977	0.804	0.836
Sensitivity (%)	100	76.0	73.7
Specificity (%)	95.4	84.7	93.5

FIB-4: fibrosis index based on four factors; APRI: aspartate aminotransferase-to-platelet ratio Index; GB: gradient boosting; PPV: positive predictive value, NPV: negative predictive value; AUROC: area under the receiver operating characteristic curve.
[a] Predetermined cutoff values of FIB-4 were used (1.45 and 3.25 to distinguish extensive fibrosis).
[b] Predetermined cutoff values of APRI were used (1.0 and 2.0 to distinguish cirrhosis).

Table 3
Diagnostic accuracy of GB-based system (LiveBoost) in predicting liver fibrosis and cirrhosis[a].

	Fibrosis	Advanced Fibrosis	Cirrhosis
AUROC	0.977	0.804	0.836
Accuracy (%)	98.2	81.7	92.1
Sensitivity (%)	100	76.0	73.7
Specificity (%)	95.4	84.7	93.5
PPV (%)	97.2	72.3	45.2
NPV (%)	100	87.1	98.0

GB: gradient boosting; PPV: positive predictive value, NPV: negative predictive value; AUROC: area under the receiver operating characteristic curve.
[a] Fleiss Kappa: 0.962, P value for Bowker <0.001.

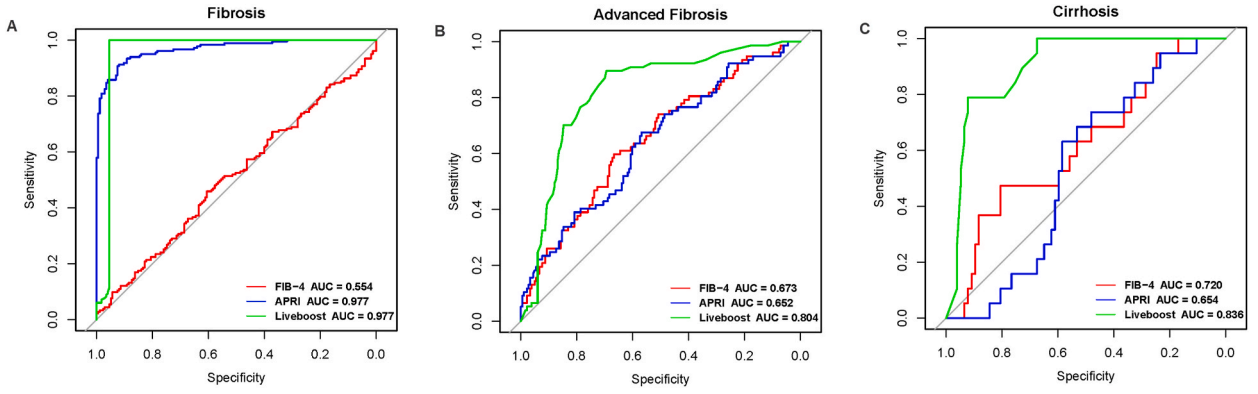

Fig. 2. Classification performances of GB-based system (LiveBoost), FIB-4 and APRI. (A) Receiver operating characteristic (ROC) curves of GB, FIB-4 and APRI for fibrosis detection; (B) ROC curves of GB, FIB-4 and APRI in advanced fibrosis; and (C) ROC curves of GB, FIB-4 and APRI in cirrhosis.

Bowker and Kappa = 0.820). The results were better in all three study sites, with AUROC of 0.804–0.849, sensitivity of 70.4%–90.9 % and specificity of 78.8%–90.5 % for advanced fibrosis (P < 0.001 for Bowker and Kappa: 0.727–0.875). The FIB-4 showed lower accuracy with a sensitivity of 59 % for the diagnosis of advanced fibrosis and a specificity of 67.2 % for excluding advanced fibrosis (cutoff value of FIB-4 >1.45).

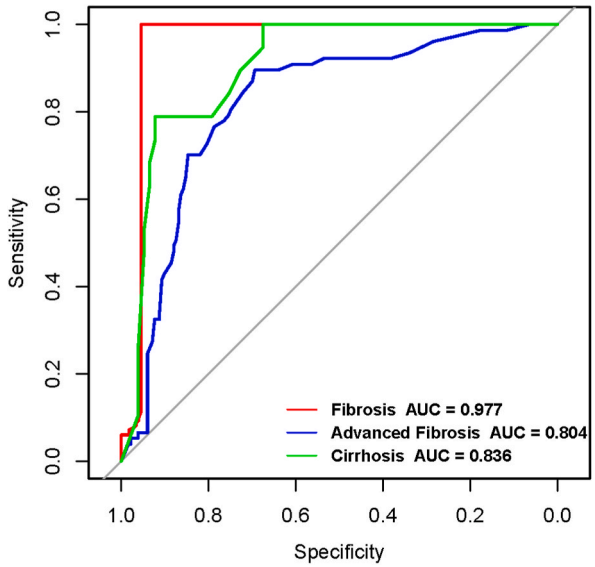

Fig. 3. Performance of LiveBoost on receiver operating characteristic (ROC) curve for liver fibrosis.

3.4. Differentiating cirrhosis vs fibrosis in CHB patients

In differentiating cirrhosis from fibrosis among CHB patients, the GB-based prediction system demonstrated the best performance with an AUROC of 0.836 (Table 2, Fig. 2C). The results showed a higher sensitivity of 73.7 % and specificity of 93.5 %. The diagnostic yield of the GB-based prediction system remained high across separate study sites (Anhui and Beijing), with AUROC ranging from 0.828 to 0.947, sensitivity of 70.00%–100 %, specificity of 89.5%–95.6 % and accuracy of 90.5%–93.9 %.

4. Discussion

Early diagnosis and accurate staging of liver fibrosis or cirrhosis are crucial for effective treatment and controlling disease progression as the prevalence of chronic liver disease increases. The gold standard for assessing liver fibrosis is liver biopsy, but non-invasive methods are desirable for convenience and patient comfort. This study aimed to compare the efficiency of the GB-based prediction system LiveBoost, the APRI and FIB-4 index with liver biopsy in the assessment of advanced liver fibrosis or cirrhosis in chronic liver disease. Previous studies have shown that APRI and FIB-4 have high reliability for predicting fibrosis or cirrhosis related to HBV, but with only moderate sensitivity and accuracy [25–31]. Our study found that the GB-based prediction system had the best performance, with significantly higher AUROCs (0.830 and 0.849) compared to APRI (0.652 and 0.654) and FIB-4 (0.673 and 0.720) in predicting advanced fibrosis and cirrhosis. Thus, we conclude that the GB-based prediction system is a superior diagnostic tool compared to APRI or FIB-4.

Machine learning, a branch of AI, serves as a screening tool to construct clinical models that predict complex phenomena from multi-dimensional data [32]. Compared to traditional regression-based methods, machine learning algorithms capture nonlinear relationships between predictors [33]. Recent studies have used machine learning methods to predict significant fibrosis and cirrhosis in CHB patients based on lab tests and ultrasound measurements [34–37].

We constructed a simple and inexpensive biomarker index, the GB-based prediction system, to identify CHB patients with liver fibrosis or cirrhosis. A previous study conducted in three Asian cohorts showed that the GB-based prediction system's AUROC and precision-recall curves for detecting advanced fibrosis or cirrhosis were higher than the FIB-4 model [20]. In this study, the GB-based prediction system showed better AUROC, sensitivity, and specificity for predicting CHB, advanced fibrosis, and cirrhosis than FIB-4 and APRI.

Several limitations of this study merit consideration. First, this is a retrospective study in three study centers, with limited sample size and ethnicity. Second, liver biopsy is used as a reference standard for evaluation of fibrosis staging, with several limitations as discussed above. Third, further prospective longitudinal studies are needed to validate the findings and predictiveness of the prediction models.

5. Conclusion

The GB-based prediction system, LiveBoost, showed improved diagnostic accuracy and better differentiation of liver fibrosis stages compared to APRI and FIB-4. Despite needing further validation, the results indicate LiveBoost is a non-invasive and easy-to-use tool with potential for liver fibrosis diagnosis and discrimination (Fig. 4).

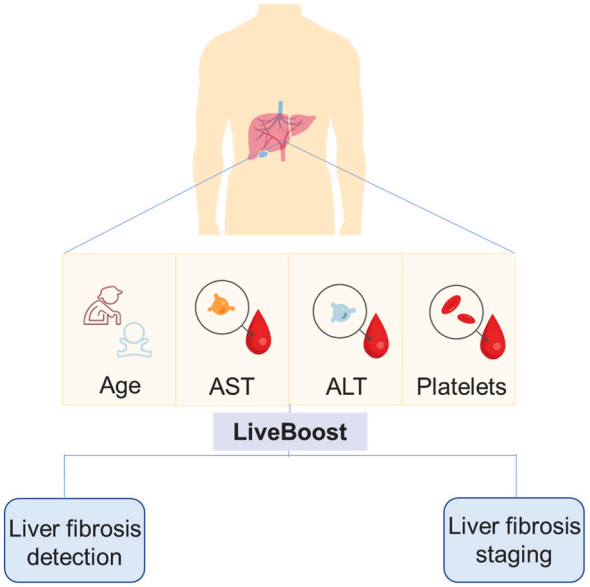

Fig. 4. LiveBoost, a more reliable and cost-effective method for assessing liver fibrosis.

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Data availability statement

Data included in article/supp. material/referenced in article.

Ethics statement

The study was approved by the ethics committees of the three participating hospitals: Guangdong Provincial Hospital of Chinese Medicine (approval no. DF2019-230-02), Second Hospital of Anhui Medical University (no. PJ-QX2020-002), and Beijing Youan Hospital (no. LL-2020-081-S). All participants provided informed consent to participate in the study.

CRediT authorship contribution statement

Guoxiang Xie: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Huanming Xiao:** Writing – review & editing, Methodology, Investigation, Data curation. **Quan Liu:** Writing – review & editing, Validation, Software, Methodology, Formal analysis. **Tianlu Chen:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **Fengyan Chen:** Writing – review & editing, Writing – original draft, Formal analysis. **Kejun Zhou:** Writing – review & editing, Methodology, Formal analysis. **Xiaoning Wang:** Writing – review & editing, Investigation, Data curation. **Ping Liu:** Writing – review & editing, Investigation, Data curation. **Zhifeng Jia:** Writing – review & editing, Software, Methodology, Formal analysis. **Lei Chen:** Writing – review & editing, Software, Methodology, Formal analysis. **Xin Deng:** Writing – review & editing, Resources, Investigation. **Fankun Meng:** Writing – review & editing, Investigation, Data curation. **Zhenhua Zhang:** Writing – review & editing, Methodology, Investigation, Data curation. **Xiaoling Chi:** Writing – review & editing, Methodology, Investigation, Data curation. **Wei Jia:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24161.

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