

World Journal of *Gastroenterology*

World J Gastroenterol 2023 April 21; 29(15): 2222-2358



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ABOUT COVER

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INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

April 21, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Retrospective Study

Value of red blood cell distribution width in prediction of diastolic dysfunction in cirrhotic cardiomyopathy

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Papazafropoulou A, Greece; Razpotnik M, Austria

Received: October 14, 2022

Peer-review started: October 14, 2022

First decision: January 3, 2023

Revised: January 27, 2023

Accepted: March 15, 2023

Article in press: March 15, 2023

Published online: April 21, 2023



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Abstract

BACKGROUND

Clinical diagnosis of cirrhotic cardiomyopathy (CCM) often encounters challenges of lack of timeliness and disease severity, with the commonly positive indicator usually associated with advanced heart failure.

AIM

To explore suitable biomarkers for early CCM prediction.

METHODS

A total of 505 eligible patients were enrolled in this study and divided into four groups according to Child-Pugh classification: Group I, Class A without CCM (105 cases); Group II, Class A with CCM (175 cases); Group III, Class B with CCM (139 cases); and Group IV, Class C with CCM (86 cases). Logistic regression and receiver operating characteristic (ROC) curve analyses were performed to determine whether red blood cell distribution width (RDW) was an independent risk factor for CCM risk. The relationships between RDW and Child-Pugh scores, Model for End-Stage Liver Disease (MELD) scores, and N-terminal pro-brain natriuretic peptide (NT-proBNP) were analyzed by Pearson correlation analysis.

RESULTS

A constant RDW increase was evident from Group I to Group IV (12.54 ± 0.85 , 13.29 ± 1.19 , 14.30 ± 1.96 , and 16.25 ± 2.13 , respectively). Pearson correlation analysis showed that RDW was positively correlated with Child-Pugh scores ($r = 0.642$, $P < 0.001$), MELD scores ($r = 0.592$, $P < 0.001$), and NT-proBNP ($r = 0.715$, $P < 0.001$). Furthermore, between Group I and Group II, RDW was the only significant index (odds ratio: 2.175, 95% confidence interval [CI]: 1.549-3.054, $P < 0.001$), and it reached statistical significance when examined by ROC curve

analysis (area under the curve: 0.686, 95%CI: 0.624-0.748, $P < 0.001$).

CONCLUSION

RDW can serve as an effective and accessible clinical indicator for the prediction of diastolic dysfunction in CCM, in which a numerical value of more than 13.05% may indicate an increasing CCM risk.

Key Words: Cirrhotic cardiomyopathy; Child-Pugh; Diagnosis; N-terminal pro-brain natriuretic peptide; Red blood cell distribution width

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Core Tip: Diastolic dysfunction is usually an early stage of cirrhotic cardiomyopathy (CCM). This study found that red blood cell distribution width would have an advantage over N-Terminal pro-brain natriuretic peptide in indicating diastolic dysfunction in such patients, which is of great significance for the early diagnosis and treatment of CCM.

Citation: Chen YL, Zhao ZW, Li SM, Guo YZ. Value of red blood cell distribution width in prediction of diastolic dysfunction in cirrhotic cardiomyopathy. *World J Gastroenterol* 2023; 29(15): 2322-2335

URL: <https://www.wjgnet.com/1007-9327/full/v29/i15/2322.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i15.2322>

INTRODUCTION

As a manifestation of unnoticeable cardiac dysfunction, cirrhotic cardiomyopathy (CCM) features diastolic dysfunction, chronotropic dysfunction, electrophysiological abnormalities, and compromised myocardial contractility in the absence of other cardiac diseases. In such a setting, liver cirrhosis-induced hyperdynamic circulation may even result in structural cardiac abnormalities[1,2]. Available literature evidences that CCM-associated diastolic dysfunction can pose very adverse clinical implications[3], including severe liver diseases, hepatorenal syndrome, ascites[4,5], and death[6]. The current clinical diagnosis of CCM-related diastolic dysfunction mainly relies on transthoracic echocardiography (TTE)[7], with N-terminal pro-brain natriuretic peptide (NT-proBNP) and other indicators playing a supportive role[8,9]. However, studies contend that NT-proBNP level is not an optimal biomarker for CCM screening and cannot serve as an independent diagnostic tool for such a condition, though increased NT-proBNP level in liver cirrhosis has been found to be positively associated with echocardiographic measures of left ventricular diastolic dysfunction (LVDD) and may be indicative of CCM[10]. Therefore, an urgent need remains regarding a more objective indicator for CCM screening in patients with LVDD, especially in the early stages of the disease.

Of all the other potential candidate indicators, red blood cell distribution width (RDW), a common blood laboratory parameter, has been closely associated with cardiac function and/or the disease severity of heart failure (HF), including the natriuretic peptides[11], left ventricular end diastolic pressure[12], and left ventricular deformation[13,14]. Meanwhile, RDW levels are more or less correlated with various liver diseases[15-18]. Studies have demonstrated that the assessment of RDW may improve risk stratification of patients with acute decompensation of cirrhosis[19]. Other studies have documented RDW as a novel inflammatory marker in various conditions, including cardiovascular diseases[20], functional bowel conditions[21], autoimmune diseases[22,23], degenerative vertebral conditions[24], malignancy[25], and even COVID-19[26]. Taken together, these findings evidence that RDW may be altered in cirrhosis patients comorbid with cardiac diastolic dysfunction and may serve as a promising objective indicator for CCM screening. Therefore, this study attempted to probe into the value of RDW in the prediction of LVDD in CCM patients.

MATERIALS AND METHODS

Patient recruitment

A single-center, retrospective study was designed to evaluate the correlation between RDW levels and liver cirrhosis with diastolic dysfunction. The clinical data of 5205 patients diagnosed with cirrhosis of various etiologies were collected between June 2017 and May 2022, and a total of 505 cases were selected and included in this study. All these patients were referred to Fujian Medical University Union Hospital

(Fuzhou, Fujian Province, China). For patients hospitalized more than once, data from the first admission were used. The following items were set to support a diagnosis of liver cirrhosis[27,28]: (1) Imaging by ultrasonography, computed tomography, or magnetic resonance imaging indicating irregular liver surface and heterogeneous liver parenchyma; (2) impaired liver synthetic function: Albumin level less than 35.0 g/L without other identifiable causes of hypoalbuminemia such as renal loss or gastrointestinal loss; and (3) evidence of portal hypertension (variceal hemorrhage, refractory ascites, or splenomegaly) or life-threatening complications such as spontaneous bacterial peritonitis or hepatic encephalopathy. Liver cirrhosis was defined as conditions meeting criteria (1) and (2) or (1) and (3).

The inclusion criteria were: (1) Age over 18 years; (2) diagnosis of cirrhosis confirmed as above mentioned; (3) severity of liver cirrhosis evaluated by Child-Pugh classification and Model for End-Stage Liver Disease (MELD) score; and (4) LVDD confirmed by TTE (controls without LVDD). The exclusion criteria were: (1) Known cardiac diseases (such as valvular heart disease, rhythm or conduction disorders, congenital heart disease, coronary artery disease, non-ischemic cardiopathy, and pulmonary arterial hypertension); (2) TTE-confirmed systolic dysfunction only; (3) other causes of liver insufficiency (such as septicemia and toxic liver disease); (4) RDW increase-related pre-existing conditions such as thalassemia, hemolytic anemia, hereditary spherocytosis, sickle cell disease, myelodysplastic syndrome, or aplastic anemia; and (5) other underlying conditions including gastric or duodenal ulcer, pregnancy, active malignancy other than liver cancer, and recent transfusion or use of iron or erythropoietin (within past 3 mo).

In particular, this study not only explored the changes of RDW in patients with CCM, but more importantly, revealed the value of RDW in predicting early CCM by comparing the differences of RDW in cirrhotic patients with or without cardiomyopathy. As a result, we set a group consisting of Child-Pugh A cirrhotic patients without CCM as the control group.

Measurements of baseline variables

Upon admission, blood samples were collected at 6 a.m. and processed immediately at the clinical laboratory of Fujian Medical University Union Hospital. The reference range of RDW was 11.5%-15.0%. Cardiac function was measured by TTE (Philips iE33, Philips Medical Systems, Andover, MA, United States). According to the latest CCM guidelines [2019 Cirrhotic Cardiomyopathy Consortium (CCC)][7], LVDD in CCM was diagnosed when three of the following conditions were present: $E/e' \geq 15$ [early diastolic transmitral and myocardial velocity on Doppler tissue imaging ratio], peak tricuspid regurgitation velocity > 2.8 m/s, septal e' velocity < 7 cm/s (early diastolic myocardial velocity on TDI), and left atrial volume index > 34 mL/m².

Spontaneous bacterial peritonitis (SBP) was defined as a bacterial infection of the ascitic fluid in the absence of a secondary intra-abdominal focus and determined by ascitic fluid polymorphonuclear (PMN) count, in which PMN count ≥ 250 cells/mm³ was diagnosed as SBP[29]. Refractory ascites was defined as ascites that cannot be mobilized or the early recurrence of which (after a large volume paracentesis) cannot be prevented by medical therapy[30]. At last, hepatic encephalopathy (HE) was defined as brain dysfunction in patients with liver failure and/or portosystemic shunts presenting cognitive alterations and personality and mental disorders[31].

Statistical analysis

The data were analyzed with SPSS version 26.0 (IBM, Somers, NY, United States). The normality of the data was evaluated by Kolmogorov-Smirnov test. For normally-distributed continuous variables, the data are presented as the mean $\pm$ SD; inter-group comparison was performed by one-way analysis of variance (ANOVA) and pairwise comparison by least significant difference *T* test (LSD-*T*). For abnormally-distributed continuous variables, data are presented as the median (interquartile range); inter-group and pairwise comparisons were analyzed by Kruskal-Wallis test and Bonferroni correction, respectively. The count data are presented as percentages (%). The proportions were measured by Chi-square test and Fisher's exact test was applied if the expected frequency was < 5 . The potential association between RDW and CCM was examined by multivariate logistic regression analysis. The discriminatory power was evaluated by the area under the receiver operating characteristic (ROC) curve (AUC) with its 95% confidence interval (CI). The statistical significance was set at a two-sided probability value of $P < 0.05$. Simultaneously, Pearson correlation analysis was used to compare the relationships between RDW and Child-Pugh scores, MELD scores, and NT-proBNP.

RESULTS

Demographic features

In addition to the 400 cases diagnosed with CCM, we matched 105 patients with early cirrhosis without cardiomyopathy. According to Child-Pugh classification[9], all 505 eligible patients were divided into four groups: Group I, Class A without CCM (control group); Group II, Class A with CCM; Group III, Class B with CCM; Group IV, Class C with CCM. The baseline demographic and clinical characteristics

of the patient cohort are shown in [Table 1](#). Patients with more serious Child-Pugh rating featured a significantly high incidence rate of hyperlipidemia and atrial fibrillation, though no statistical significance was found for age, gender, body mass index, smokers, and other demographic information among the groups.

Clinical information

The clinical symptoms, laboratory parameters, and medications of the enrolled patients are summarized in [Table 2](#). Generally, with the worsening disease severity, more obvious complications were evident from Group I to Group IV, such as haematemesis (5.7%, 6.9%, 11.5%, and 18.6%, respectively, $P = 0.009$), edema (1.9%, 6.9%, 14.4%, and 38.4%, respectively, $P < 0.001$), SBP (1%, 2.3%, 7.9%, and 15.1%, respectively, $P < 0.001$), hyponatremia (2.9%, 12%, 22.3%, and 36%, respectively, $P < 0.001$), HE (4.8%, 5.7%, 10.1%, and 22.1%, respectively, $P < 0.001$), refractory ascites (1.9%, 2.3%, 10.8%, and 24.4%, respectively, $P < 0.001$), and jaundice (11.4%, 7.4%, 23.3%, and 24.4%, respectively, $P = 0.003$). Along with the presence of these indicators, MELD score also increased in the four groups (8.74 ± 1.54 , 8.64 ± 1.57 , 17.04 ± 1.96 , and 25.19 ± 2.15 , respectively, $P < 0.001$). Except for alkaline phosphatase (ALP), regardless of the increase or decrease along with the rise of Child-Pugh level, a statistical difference was found in other laboratory indicators, such as total bilirubin (TBIL), alanine transaminase (ALT), aspartic transaminase (AST), γ -glutamyl transferase (γ -GT), albumin, white blood cell (WBC) count, hemoglobin, platelet count, international normalized ratio (INR), and estimated glomerular filtration rate (eGFR) ($P < 0.050$ for all). The frequency of administration of diuretics, anti-ventricular remodeling agents, and β -blocker increased apparently with the progression of cirrhosis ($P \leq 0.001$ for all). The clinical manifestations, laboratory indicators, and CCM medications listed in [Table 2](#) were basically consistent with the clinical practice.

RDW as an independent diagnostic indicator for CCM

The pairwise comparison of the four groups revealed a significant difference for the RDW value that rose constantly with the increasing severity of cirrhosis (12.54 ± 0.85 , 13.29 ± 1.19 , 14.30 ± 1.96 , and 16.25 ± 2.13 , $P < 0.001$) ([Table 2](#)). All indexes with $P < 0.05$ in [Tables 1](#) and [2](#) are summarized in [Table 3](#). Multivariate logistics regression analysis was divided into three parts, with the first, second, and third parts corresponding to risk factor analysis of Group II, Group III, and Group IV (Group I as the control group), respectively. Part I reported statistical significance in RDW (odds ratio [OR]: 2.175, 95%CI: 1.549-3.054, $P < 0.001$) between Group II and the control group, with no significant differences in other indicators, which suggests RDW as an independent risk factor in Part I. Part II revealed a marked difference in RDW (OR: 2.447, 95%CI: 1.375-4.354, $P = 0.002$), ALB, ALT, AST, γ -GT, WBC count, hemoglobin, platelet count, INR, NT-proBNP, and eGFR ($P < 0.05$, respectively). Further multivariate logistic regression reported significant differences in RDW (OR: 4.863, 95%CI: 2.493-9.483, $P < 0.001$), ALB, ALT, AST, WBC count, hemoglobin, platelet count, INR, NT-proBNP, and edema ($P < 0.05$, respectively), which were considered as independent risk factors in Part III. Besides, as shown in [Table 4](#), the linear regression analysis showed a positive correlation between RDW and Child-Pugh scores ($r = 0.642$, $P < 0.001$) ([Figure 1A](#)) and between RDW and MELD scores ($r = 0.592$, $P < 0.001$) ([Figure 1B](#)).

A strong correlation between RDW and different Child-Pugh levels

In [Table 2](#), due to the distribution abnormality in the data of NT-proBNP, the independent sample Kruskal-Wallis test was employed for analysis. The results showed no significant increase in NT-proBNP when the cardiomyopathy cases (Group II) were compared with the non-cardiomyopathy cases (Group I) [76 (61, 98) *vs* 72 (61, 84), $P > 0.05$] but huge differences for both Group III and Group IV ($P < 0.001$ for both). Similarly, the multivariate logistic regression reported no significant difference in NT-proBNP between Group I and Group II (OR: 1.001, 95%CI: 0.997-1.005, $P = 0.518$). The linear regression analysis ([Figure 1C](#)) further revealed a positive correlation between RDW and NT-proBNP ($r = 0.715$, $P < 0.001$) ([Table 4](#)). Finally, the ROC curve analysis was performed to determine the critical value of continuous variables (RDW and NT-proBNP) for identifying diastolic dysfunction of cardiomyopathy in cirrhosis. The criterion for the selection of optimal cut-off points was comprehensive optimization results of sensitivity and specificity. An obvious difference of P values was found for RDW and NT-proBNP ([Figure 2](#)), with a respective AUC of 0.686 (95%CI: 0.624-0.748, $P < 0.001$) and 0.556 (95%CI: 0.490-0.623, $P > 0.050$). The threshold value in ROC curves indicated that LVDD in CCM was more likely to occur if RDW was above 13.05%, with a sensitivity and specificity of 56.0% and 71.4%, respectively ([Table 5](#)).

DISCUSSION

As a chronic cardiac dysfunction, CCM is prevalent in 30%-70% of patients with cirrhosis in recent years [32,33] and features a blunted contractile response to stress and altered diastolic relaxation[34]. CCM manifests a complex progression, which depends on the systemic changes resulting from cirrhosis[35].

Table 1 Comparison of demographic and medical records in the study groups, *n* (%)

Variable	Group I (<i>n</i> = 105)	Group II (<i>n</i> = 175)	Group III (<i>n</i> = 139)	Group IV (<i>n</i> = 86)	F/ χ^2	P
Demographics						
Age (yr)	66.20 ± 7.93	67.94 ± 7.41	67.74 ± 7.84	68.00 ± 7.86	1.344	0.259
Male	65 (61.9)	95 (54.3)	82 (59.0)	56 (65.1)	3.304	0.347
Smokers	29 (27.6)	49 (28.0)	51 (36.7)	32 (37.2)	4.697	0.195
Body-mass index (kg/m ²)	23.11 ± 2.37	23.23 ± 3.95	23.75 ± 3.24	24.27 ± 3.52	2.520	0.057
Medical history						
Hypertension	20 (19.0)	32 (18.3)	35 (25.2)	26 (30.2)	6.041	0.110
Hyperlipidemia	20 (19.0)	50 (28.6)	68 (48.9)	40 (46.5)	31.658	< 0.001
Diabetes mellitus	23 (21.9)	35 (20.0)	37 (26.6)	26 (30.2)	4.146	0.246
Atrial fibrillation	8 (7.6)	36 (20.6)	52 (37.4)	34 (39.5)	38.947	< 0.001
Stroke	3 (2.9)	5 (2.9)	4 (2.9)	4 (4.7)	0.908 ¹	0.864
Cirrhosis etiology						
Fatty liver	17 (16.2)	22 (12.6)	17 (12.2)	17 (19.8)	3.277	0.351
Alcoholic liver	18 (17.1)	38 (21.7)	32 (23)	26 (30.2)	4.748	0.191
Viral hepatitis	53 (50.5)	100 (57.1)	75 (54)	36 (41.9)	5.695	0.127
Autoimmune liver disease	16 (15.2)	15 (8.6)	14 (10.1)	9 (10.5)	3.157	0.368
Liver cancer	5 (4.8)	8 (4.6)	7 (5)	4 (4.7)	0.151 ¹	1.000

¹Fisher's exact test.

Meanwhile, different criteria may indicate a distinct prevalence. A comparison between the 2005 Montreal criteria and 2019 CCC criteria[3,7] reports a higher prevalence of diastolic dysfunction by the Montreal criteria (64.8% *vs* 7.4%) and a higher proportion of cases with systolic dysfunction by the CCC criteria (16.4% *vs* 53.3%). These cases with systolic dysfunction can only be detected by echocardiography in the presence of stress[36-38]. Unlike systolic dysfunction, diastolic dysfunction appears early and can be detected at the baseline and most patients with cirrhosis display a certain degree of diastolic dysfunction[1,3,37]. Therefore, it is imminent to pinpoint some objective biomarkers before the condition deteriorates into HF.

As a traditional biomarker for the diagnosis and prognostic evaluation of HF, the clinical application of NT-proBNP is quite limited due to multiple factors[39], such as an advanced age and renal dysfunction[40]. Its effectiveness is further compromised in cases of HF with preserved ejection fraction (HFpEF), due to the impact from the clinical characteristics of HFpEF, including obesity, atrial fibrillation, and renal impairment[41]. Moreover, NT-proBNP levels may appear normal in the HFpEF patients, thereby impacting the accuracy of risk assessment[42]. Therefore, it is of great significance to find new biomarkers for the early detection of CCM.

As a hematological parameter, RDW indicates the level of anisocytosis *in vivo*. It can be assessed rapidly and economically. In acute HF patients in the emergency department (ED)[43], advanced HF patients immediately before orthotopic heart transplantation[44], and LVDD in patients with advanced stage of chronic kidney disease (CKD)[45], RDW has always been regarded as an independent predictor. Furthermore, growing evidence has confirmed an inextricable link between RDW and various types of liver-related disorders. Studies have reported the predictive value of RDW for the histological severity of primary biliary cholangitis[15] and its positive correlations with chronic hepatitis B virus infection[16, 46-48], non-alcoholic fatty liver disease[49,50], and autoimmune hepatitis[17]. Altogether, these findings lend strong support to our speculation that RDW has unique value in the diagnosis of cirrhosis.

In the current study, the regression analysis showed that RDW was the only significant indicator when Group I was compared with Group II (Table 3, Part I), which highlights that RDW is the only abnormal index in the early stage of CCM. Further linear regression analysis revealed a strong positive correlation between RDW and Child-Pugh (Figure 1A) and MELD scores (Figure 1B), indicating that RDW can serve as an evaluation index for the progression of cirrhosis. As a routine parameter of blood laboratory results, RDW is closely related to HF[11,44,51]. Although the exact underlying mechanism remains controversial, several pathophysiological mechanisms of RDW increase in HF have been proposed, such as inflammation, oxidative stress, adrenergic stimulation, undernutrition, ineffective erythropoiesis, and reduced iron mobilization[51]. Studies have speculated about the link between

Table 2 Comparison of clinical data among groups, *n* (%)

Variable	Group I (<i>n</i> = 105)	Group II (<i>n</i> = 175)	Group III (<i>n</i> = 139)	Group IV (<i>n</i> = 86)	F/ χ^2	P
Clinical feature						
Haematemesis	6 (5.7)	12 (6.9)	16 (11.5)	16 (18.6)	11.588	0.009
Edema	2 (1.9)	12 (6.9)	20 (14.4)	33 (38.4)	65.284	< 0.001
SBP	1 (1.0)	4 (2.3)	11 (7.9)	13 (15.1)	23.486	< 0.001
Hyponatremia	3 (2.9)	21 (12.0)	31 (22.3)	31 (36.0)	42.806	< 0.001
Hepatic encephalopathy	5 (4.8)	10 (5.7)	14 (10.1)	19 (22.1)	21.565	< 0.001
Refractory ascites	2 (1.9)	4 (2.3)	15 (10.8)	21 (24.4)	44.367	< 0.001
Jaundice	12 (11.4)	13 (7.4)	15 (10.8)	20 (23.3)	14.120	0.003
MELD score	8.74 ± 1.54	8.64 ± 1.57	17.04 ± 1.96 ^{a,b}	25.19 ± 2.15 ^{a,b,c}	2081.425	< 0.001
Laboratory index						
RDW (%)	12.54 ± 0.85	13.29 ± 1.19 ^a	14.3 ± 1.96 ^{a,b}	16.25 ± 2.13 ^{a,b,c}	101.958	< 0.001
TBIL (μmol/L)	12.3 (10.9, 13.45)	11.5 (9.8, 14.5)	12.8 (10.7, 17.5) ^b	16.3 (13.18, 24.95) ^{a,b,c}	57.344	< 0.001
ALB (g/L)	45.91 ± 3.83	44.92 ± 5.19 ^a	37.85 ± 4.71 ^{a,b}	33.50 ± 5.65 ^{a,b,c}	159.072	< 0.001
ALT (IU/L)	24 (18, 32)	27 (21, 34) ^a	32 (23, 37) ^{a,b}	35 (26, 75) ^{a,b,c}	40.591	< 0.001
AST (IU/L)	26 (19.5, 33)	28 (21, 35)	30 (22, 36) ^a	34 (25, 62) ^{a,b}	25.257	< 0.001
γ-GT (IU/L)	32 (20, 44)	30 (22, 41)	35 (26, 43)	37 (26, 47) ^{a,b}	14.96	0.002
ALP (IU/L)	65 (52, 84)	74 (53, 88)	69 (54, 87)	69 (58, 84)	3.535	0.316
WBC count (× 10 ⁹ /L)	5.64 ± 1.51	5.36 ± 1.40	5.76 ± 1.16 ^b	6.10 ± 1.55 ^{a,b}	5.695	0.001
Hemoglobin (g/L)	122.86 ± 15.53	121.10 ± 15.30	107.92 ± 16.33 ^{a,b}	99.28 ± 18.15 ^{a,b,c}	52.186	< 0.001
Platelet count (× 10 ⁹ /L)	190.15 ± 62.47	174.98 ± 41.71 ^a	101.09 ± 27.46 ^{a,b}	90.38 ± 32.33 ^{a,b}	165.715	< 0.001
INR	0.91 (0.59, 1.27)	1.21 (0.61, 1.80) ^a	1.58 (0.86, 2.41) ^{a,b}	1.37 (1.17, 2.22) ^{a,b}	57.797	< 0.001
NT-proBNP (pg/mL)	72 (61, 84)	76 (61, 98)	354 (127, 653) ^{a,b}	647 (364, 1430) ^{a,b,c}	242.974	< 0.001
eGFR (ml/min/1.73 m ²)	62.35 ± 11.09	60.87 ± 13.52	59.07 ± 15.94	43.31 ± 11.39 ^{a,b,c}	40.691	< 0.001
Drug information						
Diuretic	3 (2.9)	7 (4)	20 (14.4)	32 (37.2)	69.996	< 0.001
Spirolactone	3 (2.9)	7 (4)	17 (12.2)	26 (30.2)	50.491	< 0.001
ACEI/ARB	7 (6.7)	23 (13.1)	22 (15.8)	23 (26.7)	15.690	0.001
β-blocker	6 (5.7)	13 (7.4)	23 (16.5)	22 (25.6)	23.776	< 0.001

^a*P* < 0.05 when compared with Group I.^b*P* < 0.05 when compared with Group II.^c*P* < 0.05 when compared with Group III.

ACEI: Angiotensin converting enzyme inhibitor; ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine transaminase; ARB: Angiotensin receptor blocker; AST: Aspartic transaminase; eGFR: Estimated glomerular filtration rate; INR: International normalized ratio; NT-proBNP: N-terminal pro-brain natriuretic peptide; RDW: Red blood cell distribution width; SBP: Spontaneous bacterial peritonitis; TBIL: Total bilirubin; WBC: White blood cell; γ-GT: γ-glutamyl transferase.

impaired hematopoiesis and cardiac dysfunction, given the concurrent presence of increased heterogeneity of erythrocyte volume in HF patients and the contributing role of anisocytosis in the HF deterioration[52]. Meanwhile, studies have also suggested NT-proBNP as an important index for the diagnosis and evaluation of HF[39]. In the current study, the comparison of NT-proBNP between groups II, III, and IV in Table 2 showed that HFpEF deteriorated with the worsening severity of cirrhosis, which was similar to the increasing tendency of RDW in the aggravating Child-Pugh levels. Nevertheless, unlike RDW, NT-proBNP was not a percipient of cardiomyopathy in patients with Child-Pugh Class A cirrhosis, which was verified by the multiple logistic regression analysis in the first part of Table 3. In order to further expound the relationship between the two indicators, the linear regression analysis was performed between RDW and NT-proBNP (Figure 1C, Table 4), which showed that they

Table 3 Multiple logistics regression analysis for each group and the control group

Part	Variable	B	SE	Wald	P	OR (95%CI)
Part I	RDW (%)	0.777	0.173	20.141	< 0.001	2.175 (1.549, 3.054)
	TBIL (μmol/L)	-0.086	0.051	2.810	0.094	0.918 (0.83, 1.015)
	ALB (g/L)	-0.060	0.035	2.973	0.085	0.942 (0.879, 1.008)
	ALT (IU/L)	0.122	0.067	3.350	0.067	1.129 (0.991, 1.287)
	AST (IU/L)	-0.108	0.060	3.178	0.075	0.898 (0.798, 1.011)
	γ-GT (IU/L)	0.004	0.011	0.117	0.733	1.004 (0.982, 1.026)
	WBC count (× 10 ⁹ /L)	0.026	0.107	0.059	0.808	1.026 (0.832, 1.265)
	Hemoglobin (g/L)	0.012	0.010	1.294	0.255	1.012 (0.992, 1.032)
	Platelet count (× 10 ⁹ /L)	-0.006	0.003	3.638	0.056	0.994 (0.988, 1.000)
	INR	0.418	0.290	2.074	0.150	1.519 (0.86, 2.683)
	NT-proBNP (pg/mL)	0.001	0.002	0.417	0.518	1.001 (0.997, 1.005)
	eGFR (mL/min/1.73 m ²)	-0.009	0.012	0.598	0.439	0.991 (0.967, 1.015)
	Hyperlipidemia	-0.074	0.346	0.046	0.831	0.929 (0.471, 1.830)
	Atrial fibrillation	-0.402	0.602	0.448	0.503	0.669 (0.206, 2.174)
	Haematemesis	-0.730	0.711	1.054	0.305	0.482 (0.12, 1.942)
	Edema	0.105	1.196	0.008	0.930	1.111 (0.107, 11.580)
	SBP	1.623	2.242	0.524	0.469	5.07 (0.063, 410.934)
	Hyponatremia	-1.682	0.934	3.243	0.072	0.186 (0.030, 1.16)
	Hepatic encephalopathy	-0.161	0.804	0.040	0.842	0.852 (0.176, 4.119)
	Jaundice	-1.044	1.264	0.683	0.409	0.352 (0.030, 4.188)
	Refractory ascites	0.256	1.498	0.029	0.864	1.292 (0.069, 24.324)
Part II	RDW (%)	0.895	0.294	9.265	0.002	2.447 (1.375, 4.354)
	TBIL (μmol/L)	-0.028	0.083	0.116	0.733	0.972 (0.825, 1.145)
	ALB (g/L)	-0.723	0.140	26.552	< 0.001	0.485 (0.369, 0.639)
	ALT (IU/L)	0.337	0.087	15.167	< 0.001	1.401 (1.182, 1.660)
	AST (IU/L)	-0.390	0.087	19.883	< 0.001	0.677 (0.571, 0.804)
	γ-GT (IU/L)	0.037	0.018	4.313	0.038	1.037 (1.002, 1.074)
	WBC count (× 10 ⁹ /L)	0.592	0.253	5.464	0.019	1.807 (1.100, 2.969)
	Hemoglobin (g/L)	-0.057	0.026	4.929	0.026	0.944 (0.898, 0.993)
	Platelet count (× 10 ⁹ /L)	-0.055	0.010	32.104	< 0.001	0.947 (0.929, 0.965)
	INR	1.894	0.563	11.321	0.001	6.643 (2.205, 20.018)
	NT-proBNP (pg/mL)	0.008	0.003	8.203	0.004	1.008 (1.003, 1.014)
	eGFR (mL/min/1.73 m ²)	0.062	0.027	5.365	0.021	1.064 (1.010, 1.121)
	Hyperlipidemia	-1.173	0.658	3.174	0.075	0.309 (0.085, 1.125)
	Atrial fibrillation	0.365	1.006	0.132	0.717	1.441 (0.201, 10.345)
	Haematemesis	2.282	1.499	2.318	0.128	9.792 (0.519, 184.678)
	Edema	3.004	1.778	2.855	0.091	20.159 (0.618, 657.095)
	SBP	4.715	4.750	0.985	0.321	111.572 (0.010, 1231574.165)
	Hyponatremia	-0.424	1.259	0.113	0.736	0.655 (0.055, 7.724)
	Hepatic encephalopathy	-1.850	1.290	2.057	0.151	0.157 (0.013, 1.970)

Part III	Jaundice	1.862	2.392	0.606	0.436	6.437 (0.059, 699.588)
	Refractory ascites	-1.431	3.819	0.140	0.708	0.239 (0, 425.671)
	RDW (%)	1.582	0.341	21.541	< 0.001	4.863 (2.493, 9.483)
	TBIL ($\mu\text{mol/L}$)	-0.080	0.090	0.787	0.375	0.923 (0.774, 1.101)
	ALB (g/L)	-0.910	0.150	37.020	< 0.001	0.402 (0.300, 0.539)
	ALT (IU/L)	0.350	0.087	16.273	< 0.001	1.419 (1.197, 1.682)
	AST (IU/L)	-0.410	0.088	21.725	< 0.001	0.664 (0.559, 0.789)
	γ -GT (IU/L)	0.032	0.018	3.226	0.072	1.033 (0.997, 1.070)
	WBC count ($\times 10^9/\text{L}$)	0.763	0.292	6.798	0.009	2.144 (1.208, 3.803)
	Hemoglobin (g/L)	-0.070	0.029	5.697	0.017	0.932 (0.880, 0.988)
	Platelet count ($\times 10^9/\text{L}$)	-0.077	0.013	35.070	< 0.001	0.926 (0.902, 0.950)
	INR	1.828	0.621	8.661	0.003	6.224 (1.842, 21.031)
	NT-proBNP (pg/mL)	0.008	0.003	7.937	0.005	1.008 (1.002, 1.014)
	eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	-0.005	0.033	0.018	0.892	0.995 (0.932, 1.063)
	Hyperlipidemia	-0.404	0.764	0.280	0.597	0.667 (0.149, 2.986)
	Atrial fibrillation	0.417	1.132	0.135	0.713	1.517 (0.165, 13.954)
	Haematemesis	3.164	1.693	3.493	0.062	23.67 (0.857, 653.530)
	Edema	3.826	1.882	4.132	0.042	45.891 (1.147, 1836.043)
	SBP	5.570	4.815	1.339	0.247	262.503 (0.021, 3291299.144)
	Hyponatremia	-0.376	1.364	0.076	0.783	0.687 (0.047, 9.940)
	Hepatic encephalopathy	-1.949	1.468	1.763	0.184	0.142 (0.008, 2.530)
	Jaundice	0.527	2.529	0.043	0.835	1.694 (0.012, 240.821)
	Refractory ascites	-0.538	3.896	0.019	0.890	0.584 (0, 1210.714)

The multiple logistics regression reference group was Group I. Child-Pugh group assignment: Group I = 0, Group II = 1, Group III = 2, Group IV = 3. Every count indicator was set to 0 if unavailable and 1 if available. ALB: Albumin; ALT: Alanine transaminase; AST: Aspartic transaminase; eGFR: Estimated glomerular filtration rate; INR: International normalized ratio; NT-proBNP: N-Terminal pro-brain natriuretic peptide; RDW: Red blood cell distribution width; SBP: Spontaneous bacterial peritonitis; TBIL: Total bilirubin; WBC: White blood cell; γ -GT: γ -glutamyl transferase.

Table 4 Pearson correlation analysis between red blood cell distribution width and each index

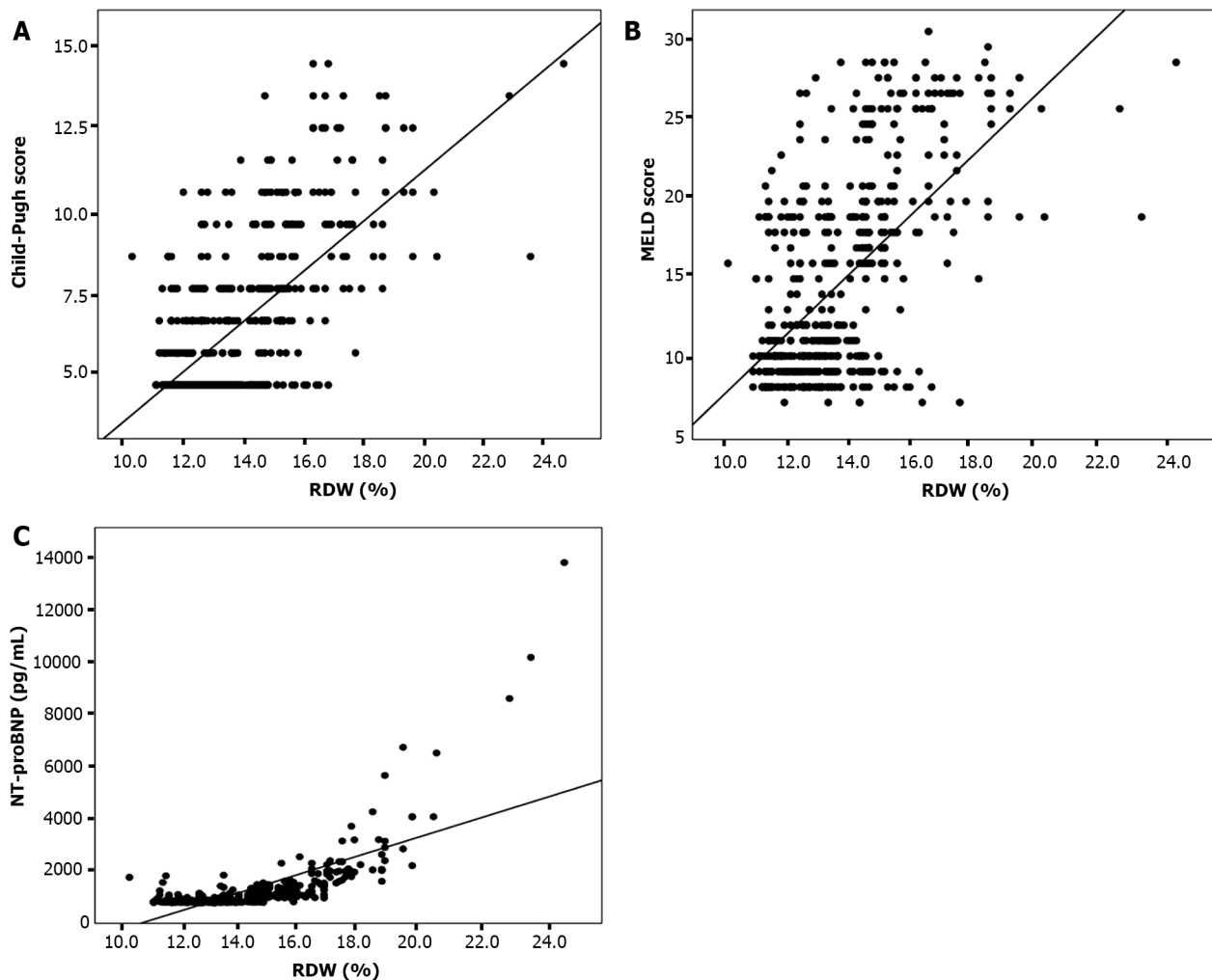
		Child-Pugh score	MELD score	NT-proBNP
RDW	<i>r</i> value	0.642	0.592	0.715
	<i>P</i> value	< 0.001	< 0.001	< 0.001

MELD score: Model for End-Stage Liver Disease score; NT-proBNP: N-terminal pro-brain natriuretic peptide; RDW: Red blood cell distribution width.

Table 5 Receiver operating characteristic curve analysis of key indexes among groups

Variable	AUC (95%CI)	SE	<i>P</i>	Critical value	Sensitivity	Specificity	Youden index
RDW	0.686 (0.624, 0.748)	0.032	< 0.001	13.05	56.0%	71.4%	0.274
NTproBNP	0.556 (0.490, 0.623)	0.034	0.114	95.50	28.0%	89.5%	0.175

AUC: Area under the curve; CI: Confidence interval; NT-proBNP: N-terminal pro-brain natriuretic peptide; RDW: Red blood cell distribution width.

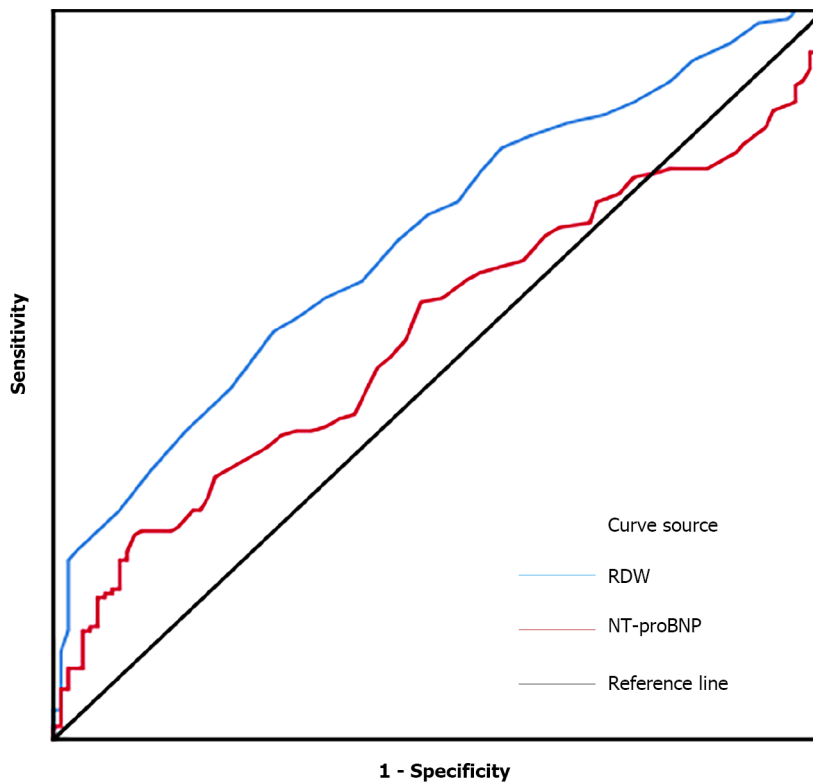


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Figure 1 Correlation. A: Correlation between red blood cell distribution width (RDW) and Child-Pugh scores; B: Correlation between RDW and Model for End-Stage Liver Disease scores; C: Correlation between RDW and N-terminal pro-brain natriuretic peptide. RDW: Red blood cell distribution width; NT-proBNP: N-terminal pro-brain natriuretic peptide.

were positively correlated with different slopes. The ROC curve analysis on this basis (Figure 2, Table 5) revealed that for mild cases of cirrhosis, the possibility of cardiomyopathy increased (sensitivity 56.0%, specificity 71.4%) when RDW was greater than 13.05%, while the change of NT-proBNP was not significant ($P = 0.114$). Taken together, these findings suggest that compared with NT-proBNP, RDW can serve as a more sensitive indicator for the early stage of CCM.

The above finding may be accounted for with the following explanations. First, cirrhosis is a chronic inflammatory disease characterized by gradual necrosis of hepatocytes, which causes a systemic inflammatory response, a slow but irreversible decline in liver function, and the development of portal hypertension[53]. On the one hand, the pathological function of the liver can increase anisocytosis and reduce erythrocyte deformability and oxygen-carrying capacity, which may further result in reduced peripheral and myocardial tissue oxygenation, contributing to HF. On the other hand, inflammatory cytokines that are closely related to cirrhosis also play an important role in the pathogenesis of HF[54], which may affect the maturation and speed of erythrocytes. Moreover, the entry of younger and larger reticulocytes into the peripheral circulation may be potential reasons for increasing RDW[50]. Still, inflammation may impair the bone marrow function, resulting in the release of premature senescent erythrocytes into the circulation and RDW increase[28,51]. Malnutrition, a common complication of liver disease, has been shown to be involved in RDW increase in HF[51]. Finally, portal hypertension due to cirrhosis can cause hemodynamic abnormalities and hypersplenism, thus accelerating the changes in erythrocyte morphology, which is inextricably linked to LVDD[4]. However, the exact mechanism awaits further exploration.



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Figure 2 Sensitivity and specificity of red blood cell distribution width and N-terminal pro-brain natriuretic peptide assessed by receiver operating characteristic curve analysis. RDW: Red blood cell distribution width; NT-proBNP: N-terminal pro-brain natriuretic peptide.

CONCLUSION

Compared with NT-proBNP, RDW displays a higher sensitivity in the prediction of LVDD in CCM, especially in forepart hepatic cirrhosis. A significant risk of CCM may be indicated if the quantitative RDW value of more than 13.05% is reported.

ARTICLE HIGHLIGHTS

Research background

Cirrhotic cardiomyopathy (CCM) was originally derived from studies of perioperative heart failure (HF) in liver transplant patients. In recent years, more and more researchers have found that not only patients undergoing liver transplantation, but also many patients diagnosed with cirrhosis will have cardiac insufficiency without other organic heart disease. CCM was often found in advanced cirrhosis.

Research motivation

At present, exact diagnostic criteria of echocardiography have been established for CCM. However, in most Chinese hospitals, due to high cost, echocardiography is not a good screening method for cases without clinical manifestations of HF. We are trying to find a proper method to predict CCM in order to achieve early detection and treatment.

Research objectives

To explore suitable biomarkers for early CCM prediction.

Research methods

We adopted the methods of data analysis. Under the premise of clear diagnostic criteria for CCM, risk factors were screened by multivariate regression analysis, and red blood cell distribution width (RDW), Child-Pugh classification, and N-terminal pro-brain natriuretic peptide (NT-proBNP) were analyzed by linear regression, and finally ROC curve analysis was performed to determine the critical value.

Research results

The possibility of cardiomyopathy increased (sensitivity 56.0%, specificity 71.4%) when RDW was greater than 13.05%, while the change of NT-proBNP was not significant ($P = 0.114$). Taken together, these findings suggest that compared with NT-proBNP, RDW can serve as a more sensitive indicator for the early stage of CCM.

Research conclusions

RDW can serve as an effective and accessible clinical indicator for the prediction of diastolic dysfunction in CCM, in which a numerical value of more than 13.05% may indicate an increasing CCM risk.

Research perspectives

First, large-scale and multi-center studies are needed to reduce the deviation error. Second, continuous hemodynamic monitoring is necessary to further analyze the hemodynamic changes in early cirrhosis.

ACKNOWLEDGEMENTS

The authors express their gratitude to the medical and technical staff of the departments of gastroenterology and cardiology who participated in this program.

FOOTNOTES

Author contributions: Guo YZ contributed to study conception and design; Chen YL contributed to data collection; Zhao ZW and Li SM contributed to data analysis; Chen YL contributed to first draft writing; Guo YZ contributed to paper review and editing.

Supported by the Fujian Provincial Education and Scientific Research Project, No. JAT200121; and Fujian Provincial Health Technology Project, No. 2021QNA021.

Institutional review board statement: All procedures involving animals were reviewed and approved by the Ethics Committee of Fujian Medical University Union Hospital (Approval No. 2022KY176).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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S-Editor: Chen YL

L-Editor: Wang TQ

P-Editor: Chen YL

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