

# Circulating IL-33/sST2 Axis and Extracellular Matrix-Related Biomarkers Across Different Ejection Fraction Phenotypes in Chronic Heart Failure

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## Research Article

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# Abstract

## Background

This study evaluated the associations of circulating interleukin-33 (IL-33), soluble ST2 (sST2), a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4), versican, and inflammatory markers with cardiac function and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with chronic heart failure (CHF), and explored their potential relevance to disease progression and phenotypic characterization.

## Methods

We enrolled 78 patients with CHF admitted between January and March 2024 and 76 concurrent healthy controls. Patients with CHF were stratified according to left ventricular ejection fraction (LVEF) into HFrEF, HFmrEF, and HFpEF groups. Serum sST2, IL-33, ADAMTS-4, versican, IL-6, and hsCRP were measured, and their associations with LVEF, left ventricular fractional shortening (LVFS), and NT-proBNP were assessed.

## Results

Serum concentrations of sST2, IL-33, ADAMTS-4, versican, IL-6, and hsCRP were significantly higher in patients with CHF than in healthy controls (all  $P < 0.05$ ). All six biomarkers were positively correlated with NT-proBNP and negatively correlated with LVEF and LVFS (all  $P < 0.05$ ). Biomarker concentrations differed significantly across HFrEF, HFmrEF, and HFpEF phenotypes; IL-33 and IL-6 differed across all pairwise phenotype comparisons (all  $P < 0.05$ ).

## Conclusions

Circulating IL-33/sST2-axis, extracellular-matrix-related, and inflammatory biomarkers are associated with NT-proBNP and left ventricular systolic function in CHF and show distinct patterns across LVEF phenotypes. These findings support further investigation of these biomarkers for clinical phenotypic characterization in larger, multicenter cohorts.

## Introduction

Chronic heart failure (CHF), the common end-stage of most cardiovascular diseases, involves a complex pathological progression that severely compromises patient prognosis and quality of life. Within the myocardium, the extracellular matrix (ECM) serves not only as a structural scaffold for maintaining tissue homeostasis but also as a critical signaling hub orchestrating cellular responses. Dynamic ECM remodeling is integral to myocardial injury repair; consequently, alterations in its composition directly

impact cardiomyocyte viability and function. Driven by chronic inflammatory stimuli (e.g., mediated by IL-6) and mechanical stress, fibroblasts may undergo phenotypic transdifferentiation, resulting in the aberrant secretion and excessive interstitial deposition of types I and III collagen. This process constitutes a hallmark pathological mechanism driving myocardial fibrosis and CHF progression <sup>[1]</sup>. Recent multi-omics studies have further highlighted that the pathogenesis of heart failure is not solely dependent on cardiomyocyte injury, but is fundamentally governed by the remodeling of the "tissue microenvironment", mediated by intricate crosstalk between immune cells and fibroblasts <sup>[2]</sup>.

Versican, a prominent ECM proteoglycan synthesized by cardiac fibroblasts, orchestrates post-injury cardiac repair by mediating the crosstalk between inflammatory cells and the extracellular microenvironment. In parallel, a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4) maintains ECM homeostasis by regulating proteoglycan turnover; its dysregulation disrupts this balance, promoting the focal accumulation of proteoglycans and collagen fibers <sup>[3]</sup>. Furthermore, the IL-33/ST2 signaling pathway, functioning as a vital paracrine axis between fibroblasts and cardiomyocytes, plays a pivotal role in modulating immune-mediated inflammation and driving myocardial fibrosis <sup>[4]</sup>. Growing evidence indicates that diverse immune cell subsets promote cardiac fibrosis and steer the cardiac remodeling trajectory via the secretion of pro-inflammatory cytokines, including IL-6, IL-1, and IL-33. Accordingly, these pro-inflammatory mediators, alongside versican, ADAMTS-4, and the IL-33/ST2 axis, represent an interconnected network that intricately drives the pathological ECM remodeling characteristic of chronic heart failure <sup>[5]</sup>.

Therefore, the present study sought to quantify the circulating concentrations of IL-33, sST2, ADAMTS-4, versican, and a key inflammatory cytokine (IL-6) in patients with CHF, and to delineate their associations with the cardiac biomarker NT-proBNP alongside echocardiographic indices of ventricular remodeling. Ultimately, this research aims to provide novel biomarker-driven evidence to refine risk stratification and therapeutic management strategies for chronic heart failure.

## Patients and Methods

### 1.1 Study Population

Patients with a confirmed diagnosis of chronic heart failure (CHF) who were admitted to the Department of Cardiology at the Third Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (West District) / Pidun District Traditional Chinese Medicine Hospital of Chengdu between January and March 2024 were enrolled as the CHF cohort. During the same period, healthy volunteers undergoing routine physical examinations at the hospital's Health Examination Center during the same period were recruited as the healthy control group. Following screening based on predefined inclusion and exclusion criteria, a total of 78 patients with CHF and 76 healthy controls were ultimately enrolled in this study.

## 2 . Inclusion Criteria

**Criteria for the CHF group:**

- (1) Fulfilled the established clinical diagnostic criteria for chronic heart failure and required inpatient hospitalization;
- (2) Availability of complete clinical data, including routine baseline, serological, and imaging evaluations;
- (3) Voluntarily provided written informed consent signed by the patients or their legal representatives.

**Criteria for the control group:**

- (1) Absence of chronic heart failure, confirmed via standardized clinical evaluation;
- (2) Completion of routine baseline and serological assessments;
- (3) Provided written informed consent prior to study participation.

### **3 . Exclusion Criteria (Applicable to All Participants)**

To minimize potential confounding effects on serological biomarkers, participants in either group were excluded if they presented with any of the following conditions:

- (1) Active acute or chronic infections, or systemic inflammatory diseases;
- (2) Severe endocrine dysfunction (e.g., hyperthyroidism);
- (3) Recent use of immunomodulatory therapy, or known autoimmune disorders (e.g., rheumatic diseases);
- (4) Severe primary comorbidities affecting the cerebrovascular, hepatic, renal, pulmonary, or hematopoietic systems;
- (5) Concomitant malignancies, history of psychiatric illnesses, or cognitive impairments that would preclude cooperation;
- (6) Refusal to participate or withdrawal of consent at any stage.

## **1.2 Laboratory Measurements and Analytical Methods**

### **1.2.1 Blood Sampling and Serological Assays**

Following overnight fasting, venous blood samples (3 mL) were collected from all participants on the morning after admission. The samples were centrifuged at 3000 rpm for 10 minutes to isolate the serum. Freshly isolated serum aliquots were immediately processed to quantify NT-proBNP levels via chemiluminescence immunoassay (CLIA), while the remaining aliquots were cryopreserved at -80°C for

subsequent batch analyses. Serum concentrations of sST2, IL-33, ADAMTS-4, versican, and IL-6 were quantified using enzyme-linked immunosorbent assay (ELISA). All assays were performed in strict adherence to the manufacturers' protocols. The optical density (OD) was recorded at a wavelength of 450 nm utilizing a microplate reader, and biomarker concentrations were extrapolated from target-specific standard curves.

## 1.2.2 Echocardiography (ECHO)

Echocardiographic evaluations were performed following standard clinical guidelines<sup>[6]</sup>. Participants were examined in the left lateral decubitus position. All scans were acquired by trained and board-certified sonographers, utilizing a Philips EPIQ-7C color Doppler ultrasound system (transducer frequency: 2.4–4.0 MHz). Key structural and functional parameters, including left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) were routinely quantified and recorded.

## 1.3 Heart Failure Phenotype Stratification

In alignment with the latest heart failure guidelines<sup>[7]</sup>, the CHF cohort was stratified into three distinct phenotypes based on echocardiographic LVEF:

- (1) Heart failure with reduced ejection fraction (HFrEF):  $LVEF < 40\%$ ;
- (2) Heart failure with mildly reduced ejection fraction (HFmrEF):  $40\% \leq LVEF < 50\%$ ;
- (3) Heart failure with preserved ejection fraction (HFpEF):  $LVEF \geq 50\%$ .

## 1.4 Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistic version 26.0. Non-normally distributed continuous variables were expressed as medians with interquartile ranges [M (P25, P75)]. Intergroup differences were evaluated using non-parametric rank-sum tests, with Bonferroni correction applied for post-hoc pairwise comparisons. Categorical variables were summarized as frequencies and percentages [n (%)], and analyzed utilizing the Chi-square ( $\chi^2$ ) test. Associations between variables were evaluated via *Spearman* rank correlation. Statistical significance was established at a two-tailed level of 0.05.

## Results

### 2.1 Baseline Characteristics of the Study Population

The CHF cohort comprised 78 patients (31 males, 47 females), with a median age of 66.00 years (IQR: 58.00–74.00; range: 19–88). Concurrently, the healthy control group consisted of 76 individuals (41 males, 35 females), with a median age of 60.00 years (IQR: 51.00–70.50; range: 23–83). The baseline demographic and clinical characteristics of all participants are summarized in Table 1.

Table 1  
Baseline characteristics of the study population

| Variables                                                                                                                                                                                                                               | CHF group ( <i>n</i> = 78) | Control group ( <i>n</i> = 76) | <i>t</i> / $\chi^2$ / <i>Z</i> value | <i>P</i> value |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|--------------------------------|--------------------------------------|----------------|
| Age, years 18–29                                                                                                                                                                                                                        | 1(33.33)                   | 2(66.67)                       | 5.547 <sup>#</sup>                   | 0.476          |
| 30–39                                                                                                                                                                                                                                   | 1(33.33)                   | 2(66.67)                       |                                      |                |
| 40–49                                                                                                                                                                                                                                   | 3(30.00)                   | 7(70.00)                       |                                      |                |
| 50–59                                                                                                                                                                                                                                   | 20(43.48)                  | 26(56.52)                      |                                      |                |
| 60–69                                                                                                                                                                                                                                   | 21(53.85)                  | 18(46.15)                      |                                      |                |
| 70–79                                                                                                                                                                                                                                   | 24(60.00)                  | 16(40.00)                      |                                      |                |
| Over 80                                                                                                                                                                                                                                 | 8(61.54)                   | 5(38.46)                       |                                      |                |
| Sex Male                                                                                                                                                                                                                                | 31(43.06)                  | 41(56.94)                      | 3.120 <sup>#</sup>                   | 0.077          |
| Female                                                                                                                                                                                                                                  | 47(57.32)                  | 35(42.68)                      |                                      |                |
| Notes: <sup>S</sup> Independent-samples <i>t</i> -test for normally distributed continuous data; * Wilcoxon rank-sum test for non-normally distributed continuous data; <sup>#</sup> Chi-square ( $\chi^2$ ) test for categorical data. |                            |                                |                                      |                |

## 2.2 Intergroup Comparison of Serological Biomarkers

Compared with healthy controls, the CHF cohort exhibited significantly elevated circulating concentrations of sST2, IL-33, ADAMTS-4, versican, IL-6, and hsCRP (all *P* < 0.05). The comprehensive biomarker profiles for both groups are detailed in Table 2.

Table 2  
Circulating biomarker profiles of the CHF and healthy control cohorts

| Variables                                                      | CHF group (n = 78) | Control group (n = 76) | Z value | P value |
|----------------------------------------------------------------|--------------------|------------------------|---------|---------|
| <b>sST2</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),pg/ml]    | 74.89(58.16,98.08) | 51.58(44.35,63.80)     | -6.606  | < 0.001 |
| <b>IL-33</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),pg/ml]   | 28.84(18.16,43.03) | 24.03(18.37,39.50)     | -2.447  | 0.014   |
| <b>ADAMTS-4 [M(P<sub>25</sub>,P<sub>75</sub>),pg/ml]</b>       | 0.95(0.59,1.51)    | 0.53(0.41,0.67)        | -6.028  | < 0.001 |
| <b>IL-6</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),pg/ml]    | 14.71(7.57,58.88)  | 0.76(0.49,1.26)        | -10.679 | < 0.001 |
| <b>hsCRP</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),mg/L]    | 9.08(4.73,13.05)   | 5.47(4.15,7.33)        | -3.748  | < 0.001 |
| <b>versican</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),ng/L] | 46.88(25.89,97.14) | 24.40(17.56,32.00)     | -4.868  | < 0.001 |

## 2.3 Correlations of Serum Biomarkers with Cardiac Function Indices and NT-proBNP

*Spearman's* rank correlation analysis revealed that circulating concentrations of sST2, IL-33, ADAMTS-4, versican, IL-6, and hsCRP in the CHF cohort were significantly and positively correlated with NT-proBNP (all  $P < 0.05$ ). Conversely, these biomarkers exhibited significant inverse correlations with echocardiographic indices of left ventricular systolic function, including LVEF and LVFS (all  $P < 0.05$ ). The respective correlation coefficients ( $r$  values) and comprehensive statistical results are detailed in Table 3.

Table 3  
Correlations of circulating biomarkers with echocardiographic indices and NT-proBNP in the CHF cohort

| <b>sST2</b>                                                           |              | <b>LVEF</b>    | <b>LVFS</b>    | <b>NT-proBNP</b> |
|-----------------------------------------------------------------------|--------------|----------------|----------------|------------------|
|                                                                       | <b>pg/ml</b> | <b>-0.811*</b> | <b>-0.786*</b> | <b>0.725*</b>    |
| <b>IL-33</b>                                                          | pg/ml        | -0.645*        | -0.598*        | 0.609*           |
| <b>ADAMTS-4</b>                                                       | pg/ml        | -0.684*        | -0.680*        | 0.616*           |
| <b>IL-6</b>                                                           | pg/ml        | -0.613*        | -0.593*        | 0.593*           |
| <b>hsCRP</b>                                                          | mg/L         | -0.699*        | -0.694*        | 0.694*           |
| <b>versican</b>                                                       | ng/L         | -0.798*        | -0.688*        | 0.688*           |
| <b>NT-proBNP</b>                                                      | pg/ml        | -0.594*        | -0.532*        | -                |
| <b>Notes:</b> * $P < 0.05$ for the correlation between two variables. |              |                |                |                  |

## 2.4 Comparison of Serological Biomarkers Across CHF Phenotypes

The *Kruskal-Wallis* test revealed significant intergroup variations in the circulating concentrations of sST2, IL-33, ADAMTS-4, versican, IL-6, and hsCRP across the three CHF phenotypes (HFrEF, HFmrEF, and HFpEF) (all  $P < 0.05$ ). Subsequent post-hoc pairwise comparisons demonstrated that levels of sST2, ADAMTS-4, versican, and hsCRP differed significantly between the HFmrEF and HFrEF groups, as well as between the HFrEF and HFpEF groups (all  $P < 0.05$ ). Notably, circulating IL-33 and IL-6 exhibited significant differences across all pairwise comparisons among the three subgroups (all  $P < 0.05$ ). The comprehensive biomarker profiles for each phenotype are detailed in Table 4.

Table 4  
Comparison of circulating biomarker concentrations among CHF subgroups stratified by LVEF phenotype

| Variables                                                                                                                  | HFrEF (n = 17)            | HFmrEF (n = 19)         | HFpEF (n = 42)           | H value | P value |
|----------------------------------------------------------------------------------------------------------------------------|---------------------------|-------------------------|--------------------------|---------|---------|
| <b>sST2</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),pg/ml]                                                                | 123.88<br>(110.56,137.59) | 56.11<br>(46.64,75.82)* | 58.90<br>(53.21,67.25)*  | 45.063  | < 0.001 |
| <b>IL-33</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),pg/ml]                                                               | 48.59<br>(42.91, 84.33)   | 26.55<br>(19.69,31.57)* | 18.55<br>(13.74,27.97)*# | 37.530  | < 0.001 |
| <b>ADAMTS-4</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),pg/ml]                                                            | 1.41<br>(1.28,1.52)       | 0.62<br>(0.43,0.90)*    | 0.63<br>(0.49,0.85)*     | 29.210  | < 0.001 |
| <b>IL-6</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),pg/ml]                                                                | 55.66<br>(47.02,58.88)    | 1.05<br>(0.56,4.94)*    | 8.53<br>(6.02,13.57)*#   | 50.022  | < 0.001 |
| <b>hsCRP</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),mg/L]                                                                | 17.66<br>(11.83,18.90)    | 6.55<br>(4.38,9.45)*    | 5.17<br>(3.59,7.30)*     | 39.964  | < 0.001 |
| <b>versican</b><br>[M(P <sub>25</sub> ,P <sub>75</sub> ),ng/L]                                                             | 350.60<br>(211.75,499.85) | 27.47<br>(19.23,51.83)* | 25.99<br>(19.06,35.10)*  | 43.231  | < 0.001 |
| <b>Notes:</b> * indicates $P < 0.05$ compared with the HFrEF group; # indicates $P < 0.05$ compared with the HFmrEF group. |                           |                         |                          |         |         |

## Discussion

The myocardial extracellular matrix (ECM)—comprising collagen fibers, matricellular proteins, and proteoglycans—serves as the structural scaffold of the heart; its dysregulation is a hallmark of ventricular remodeling. Suppression of tumorigenicity 2 (ST2), a member of the interleukin-1 (IL-1) receptor family, exists in two primary isoforms: transmembrane (ST2L) and soluble (sST2). IL-33 serves as the cognate ligand for ST2. Under physiological conditions, the binding of IL-33 to cell-surface ST2 exerts cardioprotective effects by attenuating myocardial hypertrophy, suppressing fibrosis, and reducing apoptosis [8]. Conversely, in the context of heart failure (HF), elevated ventricular wall tension triggers the upregulated secretion of sST2 from cardiomyocytes. Functioning as a "decoy receptor," sST2 competitively binds to IL-33, thereby sequestering the ligand from ST2L and blunting cardioprotective signaling; this antagonism ultimately accelerates the progression of myocardial fibrosis and ventricular remodeling [9, 10]. Multiple clinical studies have demonstrated that serum sST2 levels in HF patients are not only strongly correlated with reduced LVEF and worsening NYHA functional class [11–13], but also serve as an independent predictor of long-term all-cause mortality and rehospitalization [14]. Consistently,

our findings demonstrate that serum levels of IL-33 and sST2 in CHF patients are significantly elevated compared to healthy controls, exhibiting significant positive correlations with NT-proBNP alongside inverse correlations with LVEF. These data further underscore the clinical utility of the IL-33/sST2 axis in characterizing the pathological evolution and assessing the functional status of chronic heart failure.

The ADAMTS family, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family, plays a pivotal role in orchestrating the proteolytic regulation of ECM remodeling<sup>[15]</sup>. Notably, ADAMTS-4, primarily derived from monocyte-macrophages, mediates the targeted degradation of various ECM proteoglycans by recognizing specific cleavage sites<sup>[16, 17]</sup>. Previous research has demonstrated that ADAMTS-4 accelerates the proteolysis of the fibrous cap within atherosclerotic plaques, thereby enhancing plaque vulnerability<sup>[18, 19]</sup>. In lipopolysaccharide (LPS)-induced rat models of myocardial fibrosis, the aberrant elevation of serum ADAMTS-4 levels further implicates this enzyme in the cardiac remodeling process<sup>[20]</sup>. Jiang et al<sup>[21]</sup> reported significant upregulation of ADAMTS-4 in both the myocardium and peripheral blood of HF patients. In alignment with these observations, the present study found that circulating ADAMTS-4 levels were significantly elevated in CHF patients and exhibited a strong positive correlation with NT-proBNP, a robust indicator of heart failure severity. Collectively, these findings suggest that ADAMTS-4 may drive ventricular remodeling as a critical mediator by accelerating pathological ECM degradation, representing a promising therapeutic target.

Versican, a prominent ECM proteoglycan synthesized by cardiac fibroblasts, is critical for modulating cell adhesion, migration, and ECM assembly. In the early stages of myocardial injury, versican expression is markedly upregulated; its bioactive cleavage fragments not only promote smooth muscle cell proliferation and ECM synthesis but also bind to leukocyte surface adhesion molecules, thereby amplifying inflammatory chemotaxis<sup>[3]</sup>. Preclinical studies<sup>[22, 23]</sup> have elucidated that versican can activate integrin  $\beta 1$  and its downstream ERK1/2 signaling cascade, exerting a dichotomous effect on tissue repair and cell proliferation following myocardial infarction. Notably, ADAMTS-4 serves as the primary protease responsible for the targeted cleavage of versican<sup>[24]</sup>, intricately linking the two molecules in ECM turnover. Consistent with this mechanistic interplay, our findings demonstrate that circulating concentrations of both versican and ADAMTS-4 were significantly upregulated in the CHF cohort, and were closely associated with NT-proBNP and LVEF, robust indicators of impaired cardiac function. This suggests that in the pathogenesis of CHF, ADAMTS-4-mediated aberrant versican proteolysis not only compromises the physical homeostasis of the myocardial scaffold but also serves as a key biochemical nexus driving myocardial interstitial fibrosis and pathological remodeling by triggering systemic immune-mediated inflammatory responses.

Furthermore, chronic activation of the immune microenvironment and systemic inflammatory responses underpin the entire disease continuum of CHF<sup>[25, 26]</sup>. Beyond the conventional marker NT-proBNP, the prognostic utility of circulating biomarkers such as sST2 and hsCRP in HF risk stratification has gained substantial recognition<sup>[27]</sup>. It is widely acknowledged that the sustained upregulation of pro-inflammatory mediators, including IL-6 and hsCRP, can directly exacerbate myocardial injury and

accelerate the clinical trajectory of heart failure <sup>[28]</sup>. Building upon our previous work—which demonstrated elevated circulating inflammatory markers (IL-6 and hsCRP) in patients with rheumatic heart disease complicated by heart failure—the present study validates these observations in a broader CHF cohort. Specifically, we confirm that circulating IL-6 and hsCRP concentrations are significantly elevated in CHF patients and exhibit robust inverse correlations with LVEF. This further substantiates the pivotal role of immune-mediated systemic inflammation in the pathogenesis and progression of heart failure.

In the phenotype-stratified analysis, circulating levels of sST2, IL-33, ADAMTS-4, versican, IL-6, and hsCRP differed significantly among patients with HFrEF, HFmrEF, and HFpEF. Notably, IL-33 and IL-6 showed significant differences across all three LVEF phenotypes, suggesting that these inflammatory biomarkers may be associated with differences in cardiac functional status. In addition, the observed variations in sST2, ADAMTS-4, versican, and hsCRP across selected phenotype comparisons further indicate that inflammatory activity and extracellular matrix remodeling may differ according to the degree of left ventricular systolic dysfunction. However, these findings should be interpreted cautiously because of the relatively small sample sizes, particularly in the HFrEF and HFmrEF subgroups. Larger, multicenter studies are warranted to confirm the reproducibility of these biomarker patterns and to evaluate their potential value in heart failure phenotyping.

In summary, this study identified distinct circulating profiles of IL-33, sST2, ADAMTS-4, versican, IL-6, and hsCRP in patients with chronic heart failure. These biomarkers were significantly associated with NT-proBNP, LVEF, and LVFS, and several showed differences among HFrEF, HFmrEF, and HFpEF phenotypes. Taken together, these findings suggest that alterations in the IL-33/sST2 axis, systemic inflammation, and extracellular matrix-related biomarkers may accompany worsening cardiac function and different heart failure phenotypes. The present results support further investigation of these circulating biomarkers as potential indicators of disease severity and phenotypic characteristics in chronic heart failure. Prospective studies with larger sample sizes and external validation are required to determine their prognostic and clinical utility.

## **Declarations**

### **Ethics Statement**

This study was approved by the Ethics Review Committee of Chengdu Pidu District Hospital of Traditional Chinese Medicine (approval no. K-2023-027). Written informed consent was obtained from all participants or their legal representatives before enrollment.

## **Consent for publication**

Not applicable.

# Competing interests

The authors declare that they have no competing interests.

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# Author Contribution

YLQ and DY contributed to conceptualization, writing – review and editing, and project administration. DY, XNS, and SH contributed to writing – original draft. AHL, LY, YH, QS, ZYW, JL, ZYC, and WC contributed to visualization and resources. LRK and GTZ contributed to supervision, funding acquisition, and project administration. All authors read and approved the final manuscript.

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Not applicable.

# Data Availability

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

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