Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Serum Levels of TNFAIP3 and NLRP3 as Novel Biomarkers for Major Adverse Cardiovascular Events in Patients with Chronic Heart Failure: A Cohort Study

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Purpose: Chronic heart failure (CHF) is a major public health issue with high morbidity and mortality, where inflammation plays a key role in its progression. Tumor necrosis factor alpha-induced protein 3 (TNFAIP3) and NOD-like receptor protein 3 (NLRP3) regulate inflammatory responses, but their prognostic value in CHF remains unclear. This study aims to investigate the association between serum levels of TNFAIP3 and NLRP3 and the risk of major adverse cardiovascular events (MACEs) in patients with CHF.

Patients and Methods: A cohort study was conducted involving 318 patients with CHF and 122 controls. Serum levels of TNFAIP3 and NLRP3 were measured using enzyme-linked immunosorbent assay method. Propensity score matching (PSM) was used to control for confounders. Multivariable logistic regression, restricted cubic spline, threshold effect, and receiver operating characteristic (ROC) analyses were employed to evaluate the associations between biomarker levels and MACEs over a 6-month follow-up.

Results: After PSM, patients with CHF had significantly higher TNFAIP3 and NLRP3 levels than controls (both $p < 0.001$). Compared to CHF patients without MACEs, those with MACEs exhibited significantly lower levels of TNFAIP3 and higher levels of NLRP3. Multivariable analysis confirmed TNFAIP3 as an independent protective factor [odds ratio (OR)= 0.61, 95% confidence interval (CI): 0.40–0.93) and NLRP3 as an independent risk factor (OR = 1.24, 95% CI: 1.17–1.31) for MACEs. ROC analysis demonstrated NLRP3 (AUROC = 0.756) had better predictive ability than TNFAIP3 (AUROC = 0.611).

Conclusion: TNFAIP3 and NLRP3 are significantly associated with the risk of MACEs in patients with CHF and NLRP3 demonstrates stronger predictive performance than TNFAIP3.

Keywords: tumor necrosis factor alpha-induced protein 3, NOD-like receptor protein 3, major adverse cardiovascular events, chronic heart failure, risk stratification

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by the impairment of cardiac structure and/or function resulting from a range of underlying diseases. This impairment leads to increased cardiac pressure both at rest and during physical exertion, as well as insufficient cardiac output to meet the body's metabolic demands.[1] The incidence, prevalence, and mortality rates associated with HF remain pressing concerns in contemporary healthcare. According to the 2021 report from the European Society of Cardiology (ESC), the global prevalence of HF is continuing to rise, currently estimated to be between 1% and 3%.[1] Furthermore, the mortality rates linked to HF are notably high; studies indicate that the one-year mortality rate for patients with HF ranges from 15% to 30%,[2] while the five-year mortality rate can be as high as 50% to 70%.[2] The economic burden of HF poses significant challenges to healthcare systems worldwide and underscores the need for urgent public health interventions.[2] Therefore, it is essential to identify novel

Received: 19 September 2025
Accepted: 25 November 2025
Published: 16 December 2025

prognostic biomarkers for risk stratification in patients with HF, enabling early intervention to improve patient outcomes and alleviate the economic burden on public health.

This multifaceted condition involves changes in cardiac structure and function, dysregulation of the neuroendocrine system, and various mechanisms related to metabolism, immunity, and inflammatory responses.[3] Recent research emphasizes the critical role that inflammatory processes play in the pathophysiology of HF.[4] Zinc finger protein A20, also known as tumor necrosis factor alpha-induced protein 3 (TNFAIP3), is a highly biologically active protein encoded by the TNFAIP3 gene.[5] TNFAIP3 exhibits both ubiquitination and de-ubiquitination enzymatic activities, playing a crucial role in negatively regulating inflammatory responses and apoptosis mediated by various signaling pathways.[6] It has been implicated in the immune regulation and anti-apoptotic mechanisms of numerous diseases, including inflammatory bowel diseases, autoimmune disorders, atherosclerotic diseases, and tumors.[7–10] Another central factor in the inflammatory response, NLRP3 (nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3), senses danger signals and triggers localized and systemic inflammatory responses.[11] NLRP3 has been identified as a participant in the onset and progression of conditions such as coronary heart disease, arrhythmias, and HF.[12–14] Studies have shown that during states of inflammatory immune activation, TNFAIP3 can inhibit the expression of the NLRP3 inflammasome.[15]

Currently, research efforts are predominantly focused on the mechanisms of TNFAIP3 and NLRP3,[16–18] whereas clinical cohort studies investigating their association with the prognosis of HF remain limited. Therefore, we conducted a cohort study to investigate the association between TNFAIP3, NLRP3, and the prognosis of patients with HF. This research investigates the potential of these biomarkers for risk stratification in CHF, which may inform future strategies for early intervention and lays the groundwork for further clinical studies.

Materials and Methods

Study Design and Population

Patients diagnosed with chronic heart failure (CHF) from May 2024 to December 2024 in Qingdao Municipal Hospital were included in the study. The diagnostic criteria for CHF was based on the management guidelines published by the ESC in 2023.[19] This study enrolled patients with CHF who were in the decompensated state. All patients with CHF included in this study were diagnosed with CHF attributable to ischemic cardiomyopathy. The control group was selected from individuals undergoing routine health check-ups during the same period. These individuals had no current or historical diagnosis of HF, and were further confirmed to be free from the exclusion criteria. Patients with the following conditions were excluded: myocarditis, infectious diseases, cancer, rheumatic and immunological diseases, and stroke. The enzyme-linked immunosorbent assay (ELISA) method was used to detect the levels of TNFAIP3 and NLRP3 in the serum of the included population. Patients with CHF were followed up for six months to assess the occurrence of major adverse cardiovascular events (MACEs), and the association between TNFAIP3, NLRP3, and MACEs was analyzed. The research process is shown in Figure 1. This study was approved by the Medical Ethics Committee of Qingdao Municipal Hospital (approval number: 2024-KY-031) and strictly adhered to the Declaration of Helsinki. Written informed consent was obtained from all patients.

Sample Size and Statistical Power

An a priori sample size calculation was performed using G*Power software. Based on an odds ratio (OR) of 0.7 for TNFAIP3's protective effect, an event probability of 0.4 under the null hypothesis, an alpha of 0.05, and 80% power, a minimum of 273 participants was required. Post hoc analysis demonstrated that the study achieved 99.2% statistical power, well above the conventional 80% threshold, confirming excellent power to detect the observed association between TNFAIP3 and MACEs. Following PSM, analysis showed a large effect size (Cohen's d = 1.4) for TNFAIP3 and a statistical power exceeding 99%, indicating adequate power for post-PSM comparisons.

Data Collection

Data were obtained from laboratory tests conducted upon admission. Patient general information included age, gender and body mass index (BMI), vital signs at admission such as temperature, heart rate, respiratory rate, systolic blood

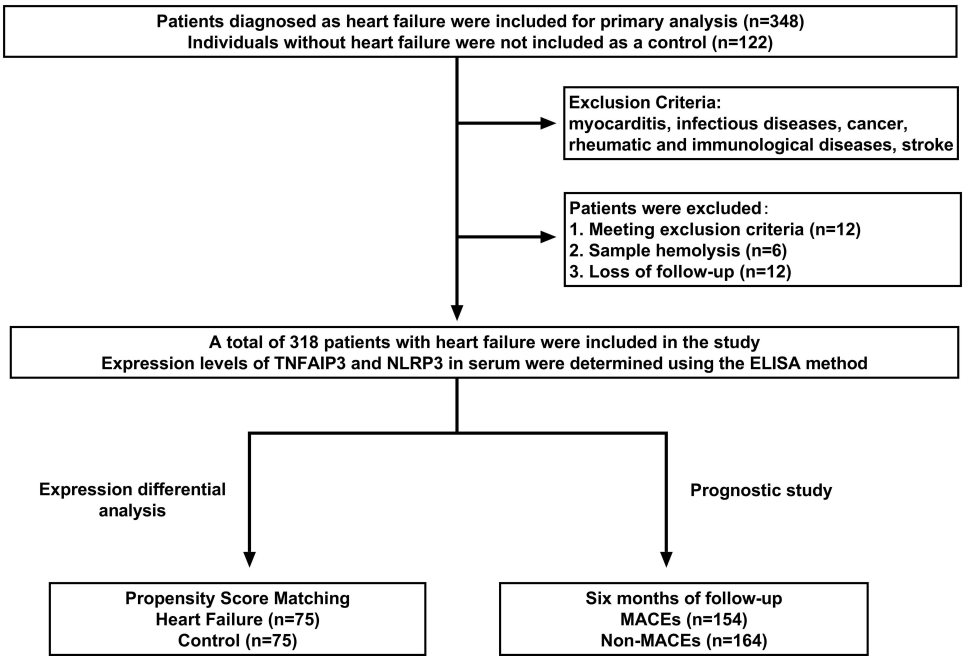

Figure 1 The flowchart of this study.

pressure (SBP), and diastolic blood pressure (DBP). Comorbidities included hypertension and type 2 diabetes mellitus (T2DM), and laboratory indicators included white blood cells (WBC), hemoglobin, albumin, C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), creatinine, uric acid, and D-Dimer. Echocardiographic indicators included fractional shortening (FS) and left ventricular ejection fraction (LVEF). The clinical severity of CHF was assessed according to the New York Heart Association (NYHA) functional classification.

Detection of TNFAIP3 and NLRP3 in Serum

Whole blood samples were allowed to stand at room temperature for 2 hours. Subsequently, they were centrifuged at 1000 g for 15 minutes and the supernatant was collected. ELISA was used to detect TNFAIP3 and NLRP3 in serum. TNFAIP3 (JL48812, Jonlnbio, Shanghai, China) and NLRP3 (JL10272, Jonlnbio, Shanghai, China) kits were strictly conducted according to the instructions provided.

Follow-Up Patients to Determine MACEs

The follow-up of patients was conducted independently by three doctors. Follow-up was conducted once a month, with a maximum follow-up period of 6 months. We recorded whether patients experienced MACEs within a 6-month period. The MACEs included cardiac death, stroke, revascularization, and rehospitalization due to HF recurrence.

Statistical Analysis

R software (version 4.3.3) and MedCalc (version 20.215) were employed for conducting the statistical analysis in this study. The Shapiro–Wilk test was conducted to evaluate the normality of the data. The results indicated that the continuous variables did not conform to a normal distribution; therefore, they were reported as medians with interquartile ranges (Q1, Q3). For the analysis of continuous variables, the Mann–Whitney *U*-test was applied. Categorical data were presented as frequencies and percentages [n (%)], with either the Chi-square test or Fisher's exact test used for comparisons. To address the disparity in group size and control for potential confounding factors between the CHF group and the non-CHF group, propensity score matching (PSM) was employed prior to comparing the levels of TNFAIP3 and NLRP3. Logistic regression models were established to explore the association between TNFAIP3, NLRP3, and MACEs. Both TNFAIP3 and NLRP3 were incorporated into the models as continuous variables and as categorical variables with three classifications. Model 1 was

unadjusted, Model 2 was adjusted for age, gender, and BMI, while Model 3 was adjusted for age, BMI, temperature, DBP, hemoglobin, albumin, CRP, NT-proBNP, D-Dimer, FS, and LVEF. To further investigate the association between TNFAIP3, NLRP3, and MACEs, we established three restricted cubic spline (RCS) models, adjusting for the same variables as in the logistic regression models. Threshold effect analysis was utilized to examine whether there is a threshold effect between TNFAIP3 and NLRP3. Receiver operating characteristic (ROC) analysis was employed to assess the predictive ability of TNFAIP3, NT-proBNP and NLRP3 for MACEs.

Results

Baseline Characteristics of the Participant Population

A total of 440 patients were included in this study, comprising 318 patients with CHF and 122 patients without CHF. The distribution of NYHA functional classes among patients with CHF was as follows: 32 patients (10.1%) were in class I, 84 patients (26.4%) in class II, 139 patients (43.7%) in class III, and 63 patients (19.8%) in class IV. In the study population, the median age was 73 years, with females accounting for 45.68% and males for 54.32%.The CHF group and the non-CHF group showed statistically significant differences in age, heart rate, respiratory rate, hemoglobin, albumin, CRP, NT-proBNP, creatinine, uric acid, D-Dimer, FS, LVEF, TNFAIP3, and NLRP3. There were no statistically significant differences in the other indicators (Table 1).

Table 1 Baseline Characteristics of Control and Heart Failure Groups

Variable	All Patients (n = 440)	Non-Heart Failure (n = 122)	Heart Failure (n = 318)	P-value
Age, (year)	73.00 (64.00, 81.00)	65.50 (58.00, 71.00)	77.00 (69.00, 83.00)	<0.001
Gender				0.362
Female, n (%)	201 (45.68)	60 (49.18)	141 (44.34)	
Male, n (%)	239 (54.32)	62 (50.82)	177 (55.66)	
BMI, (kg/m^2)	24.66 (21.97, 27.77)	25.12 (22.28, 26.80)	24.36 (21.62, 28.00)	0.597
Temperature, °C	36.40 (36.30, 36.50)	36.40 (36.30, 36.50)	36.40 (36.30, 36.50)	0.889
Heart rate, bpm	70.00 (64.00, 81.00)	69.50 (64.25, 76.00)	71.50 (64.00, 84.00)	0.040
Respiratory rate, bpm	17.00 (16.00, 18.00)	17.00 (16.00, 18.00)	17.00 (16.00, 18.00)	0.008
SBP, mmHg	133.00 (119.00, 147.25)	132.50 (121.00, 145.75)	133.00 (117.25, 149.75)	0.787
DBP, mmHg	76.00 (67.00, 85.00)	77.00 (68.00, 85.00)	76.00 (67.00, 85.00)	0.608
Hypertension, n (%)	313 (71.14)	80 (65.57)	233 (73.27)	0.111
T2DM, n (%)	153 (34.77)	36 (29.51)	117 (36.79)	0.151
WBC, 10^9/L	5.96 (5.00, 6.81)	5.81 (4.86, 6.58)	5.96 (5.05, 6.91)	0.195
Hemoglobin, g/L	128.00 (114.00, 140.00)	132.50 (124.25, 144.00)	125.50 (108.00, 139.00)	<0.001
Albumin, g/L	37.83 (35.58, 40.06)	39.66 (37.57, 41.99)	37.37 (34.85, 39.04)	<0.001
CRP, mg/L	1.35 (0.50, 2.49)	0.69 (0.50, 1.95)	1.35 (0.50, 2.66)	<0.001
NT-proBNP, pg/mL	235.00 (44.80, 937.40)	22.50 (15.00, 35.90)	517.00 (181.32, 1236.00)	<0.001
Creatinine, μmol/L	73.90 (61.88, 81.07)	65.56 (54.75, 73.90)	73.90 (66.28, 85.72)	<0.001
Uric acid, umol/L	367.68 (323.75, 407.53)	328.88 (274.85, 373.93)	367.68 (367.68, 425.25)	<0.001
D-Dimer, mg/L	0.45 (0.28, 0.62)	0.27 (0.19, 0.42)	0.45 (0.37, 0.71)	<0.001
FS, %	28.00 (20.00, 30.00)	31.00 (30.00, 31.75)	23.50 (17.00, 29.00)	<0.001
LVEF, %	55.00 (38.00, 60.00)	60.00 (60.00, 61.75)	45.00 (34.00, 57.00)	<0.001
TNFAIP3, ng/mL	0.57 (0.37, 0.85)	0.29 (0.22, 0.34)	0.68 (0.52, 0.94)	<0.001
NLRP3, ng/mL	6.88 (4.13, 12.74)	2.76 (1.87, 3.65)	10.46 (6.78, 14.22)	<0.001

Abbreviations: BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; T2DM, Type 2 Diabetes Mellitus; WBC, White Blood Cells; CRP, C-Reactive Protein; BNP, B-type Natriuretic Peptide; FS, Fractional Shortening; LVEF, Left Ventricular Ejection Fraction; TNFAIP3, Tumor Necrosis Factor Alpha Induced Protein 3; NLRP3, NOD-like receptor protein 3.

The Expression of TNFAIP3 and NLRP3 in the CHF Group

In order to compare the expression of TNFAIP3 and NLRP3 in the serum of CHF and non-CHF groups while controlling for confounding factors, we employed the PSM method. After 1:1 matching, 75 patients were matched in each group. After matching, with the exception of TNFAIP3 and NLRP3, there were no significant differences in any of the variables between the two groups, with all p-values > 0.05. TNFAIP3 levels in the CHF group were significantly higher at 0.70 ng/mL [95% confidence interval (CI): 0.52 ng/mL, 1.02 ng/mL] compared to the non-CHF group, which had a level of 0.29 ng/mL (95% CI: 0.23 ng/mL, 0.34 ng/mL). NLRP3 levels in the CHF group were significantly higher at 8.62 ng/mL (95% CI: 6.65 ng/mL, 13.26 ng/mL) compared to the non-CHF group, which had a level of 2.76 ng/mL (95% CI: 1.91 ng/mL, 3.38 ng/mL) (Table 2).

Characteristics of Patients with CHF Experiencing MACEs

Among 318 patients with CHF, a total of 154 patients ultimately experienced MACEs. The specific composition of the first occurring MACEs was as follows: rehospitalization due to HF recurrence was the most common event (n=67, 43.5%), followed by stroke (n=41, 26.6%), revascularization (including PCI n=27, 17.5%, and CABG, n=8, 5.2%), and cardiac death (n=11, 7.1%). Compared to those without MACEs, patients who experienced MACEs exhibited higher levels of age, CRP, NT-proBNP, D-Dimer, and NLRP3. Patients who experienced MACEs had lower values of BMI, temperature, DBP, hemoglobin, FS, LVEF, and TNFAIP3 (Table 3).

Results of the Logistic Regression Analysis

The association of TNFAIP3 and NLRP3 with MACEs was investigated using logistic regression models. The results indicated that TNFAIP3 was an independent protective factor for MACEs. In the crude model, the OR of TNFAIP3 was 0.61 (95% CI: 0.40–0.93, p=0.022). When TNFAIP3 was treated as a three-category variable, the

Table 2 Comparison of TNFAIP3 and NLRP3 Expression in Heart Failure Patients After Propensity Score Matching

Variable	Total (n = 150)	Non-Heart Failure (n = 75)	Heart Failure (n = 75)	P-value
Age, (year)	69.00 (61.00, 76.00)	67.00 (61.50, 73.00)	72.00 (61.00, 78.00)	0.061
Gender				0.870
Female, n (%)	77 (51.33)	39 (52.00)	38 (50.67)	
Male, n (%)	73 (48.67)	36 (48.00)	37 (49.33)	
BMI, (kg/m^2)	25.09 (22.36, 27.34)	24.80 (22.23, 26.45)	25.47 (22.57, 28.66)	0.072
Temperature, °C	36.40 (36.30, 36.50)	36.40 (36.30, 36.50)	36.30 (36.30, 36.50)	0.821
Heart rate, bpm	70.00 (63.00, 78.00)	70.00 (65.00, 76.50)	68.00 (60.00, 79.00)	0.464
Respiratory rate, bpm	17.00 (16.00, 18.00)	17.00 (16.00, 18.00)	17.00 (16.00, 18.00)	0.521
SBP, mmHg	136.00 (122.00, 147.00)	133.00 (121.50, 146.50)	137.00 (123.00, 148.00)	0.687
DBP, mmHg	78.00 (69.00, 85.00)	77.00 (69.00, 83.50)	78.00 (68.50, 86.00)	0.801
Hypertension, n (%)	110 (73.33)	53 (70.67)	57 (76.00)	0.460
T2DM, n (%)	44 (29.33)	20 (26.67)	24 (32.00)	0.473
WBC, 10^9/L	5.87 (4.84, 6.59)	5.82 (5.00, 6.53)	5.89 (4.80, 6.63)	0.879
Hemoglobin, g/L	131.00 (124.00, 142.75)	131.00 (124.00, 140.50)	131.00 (123.00, 145.00)	0.785
Albumin, g/L	38.44 (37.27, 41.54)	38.60 (37.12, 41.22)	38.38 (37.48, 41.67)	0.987
CRP, mg/L	0.78 (0.50, 1.93)	0.77 (0.50, 2.17)	0.79 (0.50, 1.35)	0.453
Creatinine, μmol/L	68.94 (57.32, 75.51)	66.51 (55.44, 74.12)	71.68 (58.46, 76.90)	0.340
Uric acid, umol/L	366.10 (283.46, 373.72)	348.17 (280.54, 378.39)	367.68 (303.49, 367.68)	0.913
D-Dimer, mg/L	0.31 (0.22, 0.45)	0.30 (0.20, 0.47)	0.36 (0.22, 0.45)	0.379
TNFAIP3, ng/mL	0.43 (0.29, 0.69)	0.29 (0.23, 0.34)	0.70 (0.52, 1.02)	<0.001
NLRP3, ng/mL	4.47 (2.76, 8.59)	2.76 (1.91, 3.38)	8.62 (6.65, 13.26)	<0.001

Abbreviations: BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; T2DM, Type 2 Diabetes Mellitus; WBC, White Blood Cells; CRP, C-Reactive Protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; FS, Fractional Shortening; LVEF, Left Ventricular Ejection Fraction; TNFAIP3, Tumor Necrosis Factor Alpha Induced Protein 3; NLRP3, NOD-like receptor protein 3.

https://doi.org/10.2147/JIR.S567963

Table 3 Characteristics Between Heart Failure Patients with MACEs and Those Without MACEs

Variable	Heart Failure Patients (n = 318)	Non-MACEs (n = 164)	MACEs (n = 154)	P-value
Age, (year)	77.00 (69.00, 83.00)	72.00 (62.75, 80.00)	80.00 (75.00, 85.00)	<0.001
Gender				0.129
Female, n (%)	141 (44.34)	66 (40.24)	75 (48.70)	
Male, n (%)	177 (55.66)	98 (59.76)	79 (51.30)	
BMI, (kg/m^2)	24.36 (21.62, 28.00)	25.54 (22.49, 28.69)	23.66 (20.71, 27.63)	<0.001
Temperature, °C	36.40 (36.30, 36.50)	36.40 (36.30, 36.50)	36.30 (36.20, 36.50)	0.022
Heart rate, bpm	71.50 (64.00, 84.00)	73.00 (64.75, 88.00)	70.00 (64.00, 80.00)	0.176
Respiratory rate, bpm	17.00 (16.00, 18.00)	17.00 (16.00, 18.00)	17.00 (16.00, 18.00)	0.464
SBP, mmHg	133.00 (117.25, 149.75)	135.50 (116.00, 150.25)	132.00 (119.25, 146.75)	0.410
DBP, mmHg	76.00 (67.00, 85.00)	79.00 (70.00, 87.00)	73.00 (64.00, 80.00)	<0.001
Hypertension, n (%)	233 (73.27)	119 (72.56)	114 (74.03)	0.768
T2DM, n (%)	117 (36.79)	58 (35.37)	59 (38.31)	0.586
WBC, 10^9/L	5.96 (5.05, 6.91)	6.06 (5.29, 6.92)	5.78 (4.88, 6.81)	0.088
Hemoglobin, g/L	125.50 (108.00, 139.00)	131.00 (120.00, 144.00)	116.00 (99.25, 129.75)	<0.001
Albumin, g/L	37.37 (34.85, 39.04)	37.83 (35.71, 40.29)	36.53 (33.04, 37.83)	<0.001
CRP, mg/L	1.35 (0.50, 2.66)	1.24 (0.50, 2.27)	1.35 (0.97, 3.33)	0.005
NT-proBNP, pg/mL	517.00 (181.32, 1236.00)	266.00 (143.30, 916.10)	857.00 (375.40, 2200.00)	<0.001
Creatinine, μmol/L	73.90 (66.28, 85.72)	73.90 (66.04, 84.38)	73.90 (66.84, 86.02)	0.741
Uric acid, umol/L	367.68 (367.68, 425.25)	367.68 (367.68, 436.35)	367.68 (364.37, 404.34)	0.087
D-Dimer, mg/L	0.45 (0.37, 0.71)	0.45 (0.33, 0.62)	0.45 (0.45, 0.82)	<0.001
FS, %	23.50 (17.00, 29.00)	25.00 (18.00, 30.00)	22.00 (17.00, 28.00)	0.043
LVEF, %	45.00 (34.00, 57.00)	48.00 (35.00, 58.00)	41.00 (32.75, 55.00)	0.038
TNFAIP3, ng/mL	0.68 (0.52, 0.94)	0.75 (0.57, 1.12)	0.64 (0.49, 0.87)	<0.001
NLRP3, ng/mL	10.46 (6.78, 14.22)	7.12 (5.63, 11.74)	13.18 (10.48, 15.43)	<0.001

Abbreviations: BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; T2DM, Type 2 Diabetes Mellitus; WBC, White Blood Cells; CRP, C-Reactive Protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; FS, Fractional Shortening; LVEF, Left Ventricular Ejection Fraction; TNFAIP3, Tumor Necrosis Factor Alpha Induced Protein 3; NLRP3, NOD-like receptor protein 3.

OR for T3 was 0.38 (95% CI: 0.22–0.66, p<0.001). After adjusting for covariates, TNFAIP3 remained an independent protective factor. In the crude model, the OR for NLRP3 was 1.24 (95% CI: 1.17–1.31, p<0.001). When NLRP3 was treated as a three-category variable, the OR for T3 was 8.20 (95% CI: 4.40–15.26, p<0.001). In Model 2 and Model 3, NLRP3 remained an independent risk factor (Figure 2).

Nonlinear Associations of TNFAIP3 and NLRP3 with MACEs

RCS regression with multivariable-adjusted associations was utilized to demonstrate the dose-response associations between TNFAIP3, NLRP3, and the prevalence of MACEs. The results indicated a negative nonlinear correlation

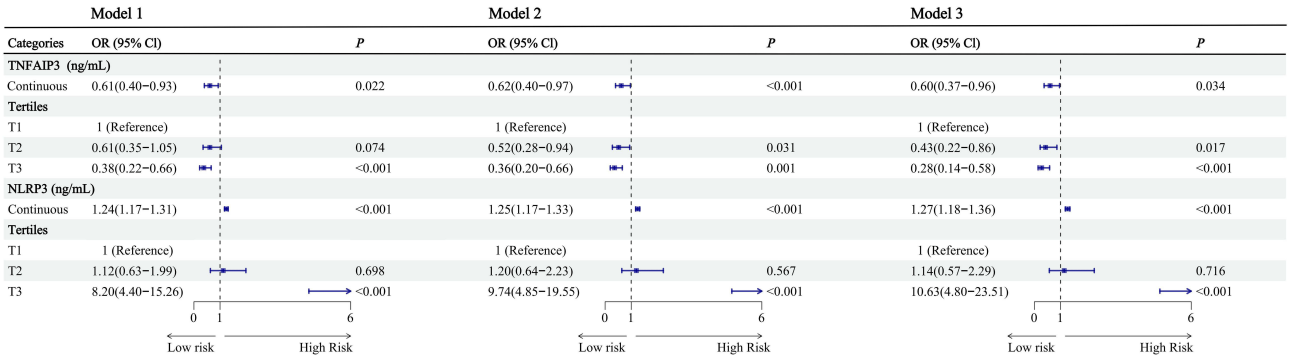

Figure 2 Logistic regression models predicting the occurrence of MACEs in patients with heart failure. Model 1: unadjusted. Model 2: adjusted for age, gender, and Body Mass Index. Model 3: adjusted for age, Body Mass Index, Temperature, Diastolic Blood Pressure, Hemoglobin, Albumin, C-Reactive Protein, N-terminal pro-B-type natriuretic peptide, D-Dimer, Fractional Shortening and Left Ventricular Ejection Fraction.

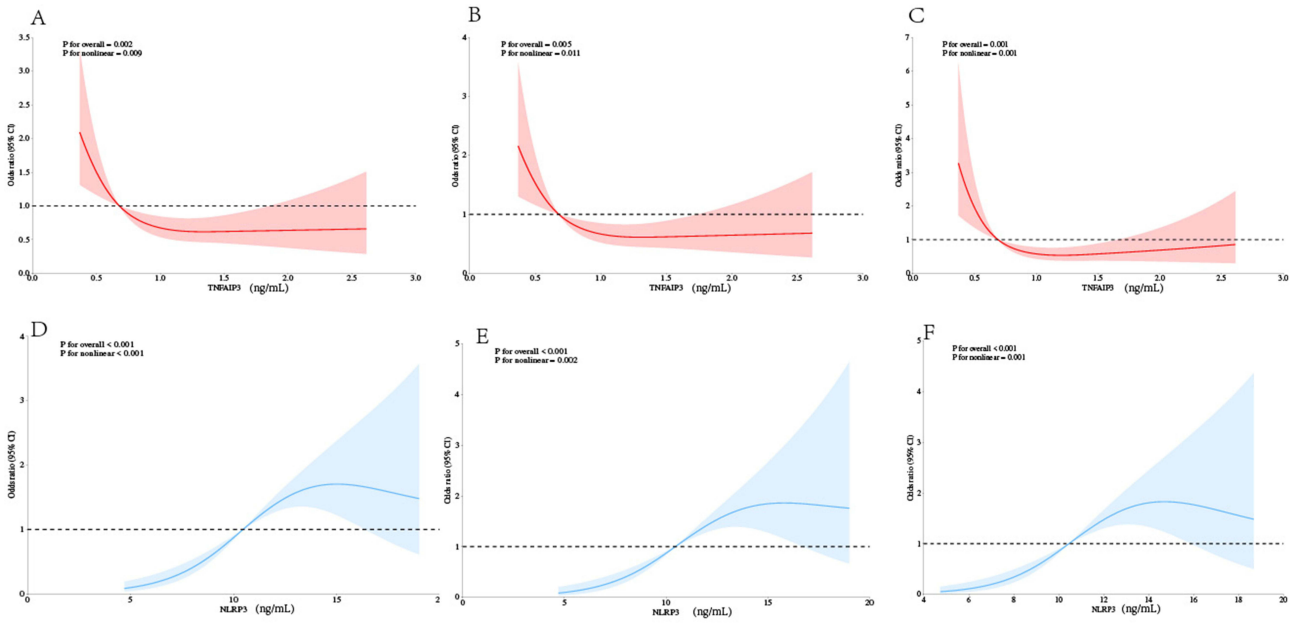

Figure 3 Restricted cubic spline models. RCS regression with multivariable-adjusted associations was utilized to demonstrate the dose-response associations between TNFAIP3 (**A**–**C**) NLRP3 (**D**–**F**) and the prevalence of MACEs.

between TNFAIP3 and MACEs (p for nonlinear = 0.009). This association persisted after adjusting for covariates. Conversely, a positive nonlinear correlation was observed between NLRP3 and MACEs (p for nonlinear < 0.001), which also remained evident after adjusting for covariates (Figures 3).

Threshold Effect Analysis

The TNFAIP3 exhibited a threshold effect in relation to the incidence of MACEs (p for likelihood test = 0.003). Overall, there is a negative association between TNFAIP3 and MACEs (OR: 0.61, 95% CI 0.40–0.93, p = 0.022). Specifically, no association was found between TNFAIP3 and MACEs when TNFAIP3 values were above 1.76. In contrast, when TNFAIP3 below 1.76, a negative association emerged between TNFAIP3 and MACEs (OR: 0.23, 95% CI 0.10–0.52, p < 0.001) (Table 4). The NLRP3 exhibited a threshold effect in relation to the incidence of MACEs (p for likelihood test < 0.001). Overall, there was a positive association between NLRP3 and MACEs (OR: 1.24, 95% CI 1.17–1.31, p < 0.001). Specifically, no association was found between NLRP3 and MACEs when NLRP3 values were below 6.61. In contrast, when NLRP3 was above 6.61, a positive association emerged between NLRP3 and MACEs (OR: 1.13, 95% CI 1.06–1.20, p < 0.001) (Table 5).

Table 4 Threshold Effect Analysis of TNFAIP3 on MACEs Using a Two-Piecewise Logistic Regression

TNFAIP3	OR (95% CI)	*P*
Model I Fitting model by standard linear regression	0.61 (0.40–0.93)	0.022
Model 2 Fitting model by two-piecewise logistic regression		
Inflection point	1.76	
<1.76	0.23 (0.10–0.52)	<0.001
≥1.76	2.96 (0.69–12.72)	0.145
P for likelihood test		0.003

Abbreviations: MACEs, Major adverse cardiovascular events; TNFAIP3, Tumor necrosis factor alpha induced protein 3; OR, Odds ratio; CI, Confidence interval.

https://doi.org/10.2147/JIR.S567963

Table 5 Threshold Effect Analysis of NLRP3 on MACEs Using a Two-Piecewise Logistic Regression

NLRP3	OR (95% CI)	*P*
Model 1 Fitting model by standard linear regression	1.24 (1.17–1.31)	<0.001
Model 2 Fitting model by two-piecewise logistic regression		
Inflection point	6.61	
<6.61	1.05 (0.92–1.20)	0.451
≥6.61	1.13 (1.06–1.20)	<0.001
P for likelihood test		<0.001

Abbreviations: MACEs, Major adverse cardiovascular events; NLRP3, NOD-like receptor protein 3; OR, Odds ratio; CI, Confidence interval.

Comparison of the Predictive Abilities of TNFAIP3, NT-proBNP and NLRP3 for MACEs

The ROC curve was used to compare the predictive abilities of TNFAIP3, NT-proBNP and NLRP3 for MACEs (Figure 4). The results showed that NLRP3 outperformed TNFAIP3 [Area under the ROC (AUROC): 0.756 vs 0.611, Delong's test]. Although the AUROC of NLRP3 was slightly higher than that of NT-proBNP, there was no statistically significant difference. This indicated that NLRP3 has predictive efficacy comparable to NT-proBNP (Table 6).

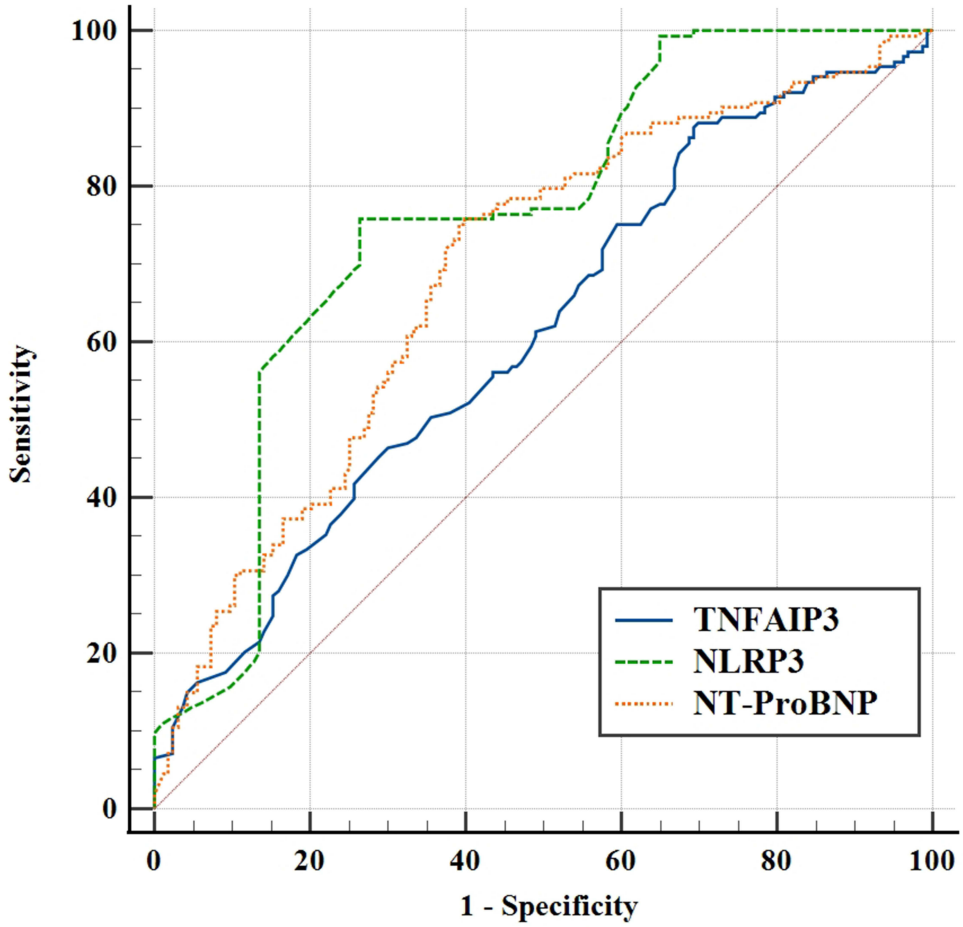

Figure 4 Receiver operating characteristic analysis comparing the predictive ability of TNFAIP3, NT-proBNP and NLRP3 for MACEs.

Table 6 The Predictive Ability of TNFAIP3, NLRP3, and NT-proBNP for the Risk of MACEs

Comparison of Two Variables	AUCs	Difference in AUROC	DeLong's Test
TNFAIP3 vs NT-proBNP	0.611 vs 0.688	0.077	P = 0.079
NLRP3 vs NT-proBNP	0.756 vs 0.688	0.068	P = 0.092
NLRP3 vs TNFAIP3	0.756 vs 0.611	0.145	P < 0.001

Abbreviations: TNFAIP3, Tumor Necrosis Factor Alpha Induced Protein 3; NLRP3, NOD-like receptor protein 3; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MACEs, Major adverse cardiovascular events; AUC, Area Under the Curve; AUROC, Area Under the Receiver Operating Characteristic Curve.

Discussion

In this cohort study, we investigated the association between serum TNFAIP3, NLRP3 levels, and the prognosis of patients with CHF. Our key findings were as follows: First, compared with the non-CHF group, the serum levels of both TNFAIP3 and NLRP3 in the CHF group were significantly higher. Second, among patients with CHF, those who experienced MACEs had lower TNFAIP3 levels and higher NLRP3 levels compared to those without MACEs. Logistic regression analysis further revealed that TNFAIP3 was an independent protective factor for MACEs in patients with CHF, while NLRP3 was an independent risk factor, and these associations remained significant after adjusting for multiple covariates. Finally, ROC analysis indicated that NLRP3 had a better predictive ability for MACEs than TNFAIP3, with an AUROC of 0.756 versus 0.611. These findings collectively suggested that TNFAIP3 and NLRP3 may play important roles in the progression and prognosis of CHF, with potential value in risk stratification and prognostic assessment of patients with CHF.

This study observed a significant age difference between the CHF and non-CHF groups, which aligns with the epidemiological characteristic that CHF is more prevalent in the elderly population.[2] Age-related physiological changes may potentially influence the serum levels of these two biomarkers. However, multiple strategies were employed to minimize this confounding effect. Firstly, PSM effectively balanced age and other baseline variables between the two groups, with no significant age difference observed in the matched cohort ($p = 0.061$). Secondly, age was included as a key covariate in the multivariable regression models to adjust for its potential influence on the prognostic value of the biomarkers. Collectively, these measures confirm that the significant differences in TNFAIP3 and NLRP3 levels between the CHF and non-CHF groups, as well as their prognostic significance for MACEs, are not primarily confounded by age.

The levels of TNFAIP3 and NLRP3 were significantly elevated in patients with CHF than those without CHF, indicating that both proteins play a role in the pathophysiological processes associated with CHF. During the progression of CHF, myocardial injury triggers a stress response that activates the body's inflammatory pathways.[20,21] As a critical "sensor" in these inflammatory responses, the increased level of NLRP3 suggests heightened inflammasome activation, which further amplifies the inflammatory cascade and promotes the release of pro-inflammatory cytokines such as IL-1β and IL-18.[22,23] This, in turn, exacerbates myocardial cell injury and ventricular remodeling.[22,23] Simultaneously, the concurrent elevation of TNFAIP3 may indicate a compensatory protective mechanism against excessive inflammation.[24,25] Through its dual enzymatic activities of ubiquitination and de-ubiquitination, TNFAIP3 negatively regulates inflammatory signaling pathways, aiming to halt the uncontrolled spread of inflammation.[26,27] The dynamic variations of both proteins collectively illuminate the imbalance in inflammatory homeostasis found in patients with CHF.

From a mechanistic viewpoint, our findings can be interpreted through the interplay between these two biomarkers in the inflammatory cascade of CHF. TNFAIP3, as a key negative regulator of inflammation, is known to inhibit the activation of the NF-κB signaling pathway, thereby mitigating the release of pro-inflammatory factors and alleviating myocardial inflammatory damage.[28–30] A study further demonstrated that the A20-NF-κB pathway plays a critical role in cardio-protection against inflammatory injury.[31] Additionally, TNFAIP3 may suppress cardiomyocyte apoptosis, thereby preserving the structural and functional integrity of the myocardium.[32,33] A related protein, TNIP3 (TNFAIP3 interacting protein 3), has been shown to protect against pathological cardiac hypertrophy by stabilizing STAT1,[34] suggesting the broader importance of this protein family in cardiac homeostasis. Conversely, sustained high expression of NLRP3 facilitates the assembly of the inflammasome, leading to the excessive generation of potent pro-inflammatory cytokines such as IL-1β and IL-18, which accelerates myocardial fibrosis

and compromises cardiac function.[35,36] NLRP3 inflammasome activation has been identified as a key mechanism in the pathogenesis of various cardiac conditions, including pressure overload-induced cardiac hypertrophy[14] and dilated cardiomyopathy.[37] The association between higher risk, lower TNFAIP3, and higher NLRP3 suggests an imbalance in this inflammatory checkpoint system in CHF. Future studies combining myocardial tissue analysis with molecular biological experiments are warranted to further elucidate the precise interaction between TNFAIP3 and NLRP3 in the pathophysiology of CHF.

Moreover, RCS analysis demonstrated a non-linear association of both TNFAIP3 and NLRP3 with MACEs. Threshold effect analysis identified critical values of 1.76 ng/mL and 6.61 ng/mL, respectively, providing quantitative benchmarks for risk stratification. Clinically, TNFAIP3 levels below 1.76 ng/mL or NLRP3 levels exceeding 6.61 ng/mL are associated with higher risk and should prompt an intensified monitoring protocol, including closer follow-up intervals and enhanced surveillance of vital signs such as blood pressure and heart rate. Therapeutically, this high-risk association justifies an escalated treatment strategy, which involves optimizing guideline-directed medical therapy by up-titrating anti-heart failure medications and, for medication-intolerant patients, evaluating the indication for device-based interventions.

ROC curve analysis demonstrated that NLRP3's predictive performance for MACEs (AUROC=0.756) was significantly superior to that of TNFAIP3 (AUROC=0.611). This indicated that NLRP3 may serve as a more optimal biomarker for prognostic evaluation in patients with CHF. This may be related to the central role of NLRP3 in the initiation and amplification of inflammatory processes, with its level changes more sensitively reflecting the activity of the inflammatory response and the progression trend of the disease in patients with CHF. In contrast, TNFAIP3, as a compensatory protective factor, may be regulated by various factors, leading to relatively lower predictive specificity. Furthermore, several inflammatory cytokines, such as IL-6[38,39] and IL-1β,[40,41] have been well-established as biomarkers associated with the prognosis of CHF. Our study addresses a knowledge gap by focusing on the upstream regulatory proteins within these inflammatory pathways. Future research should directly compare the prognostic value of these upstream regulators with that of the downstream cytokines.

This study had a follow-up period of 6 months, which validated the association between TNFAIP3/NLRP3 and short-term MACEs but did not establish their predictive value for the long-term prognosis (eg, 1-year or 5-year mortality or long-term MACEs) of patients with CHF. However, from a pathophysiological perspective, short-term serum TNFAIP3/NLRP3 levels may still provide important clues to long-term outcomes. Firstly, the core of CHF progression is a persistent inflammatory imbalance.[21] Inadequate anti-inflammatory regulation mediated by TNFAIP3 and chronic overactivation of the NLRP3 inflammasome can continuously drive myocardial fibrosis, ventricular remodeling, and the deterioration of cardiac function.[35,42] Therefore, the disruption of inflammatory homeostasis, as indicated by abnormal short-term biomarker levels, could represent an "early signal" of long-term disease progression. Secondly, the synergistic associations between TNFAIP3/NLRP3 and traditional prognostic indicators like NT-proBNP observed in our study are noteworthy. Given that NT-proBNP itself is a well-established predictor of long-term outcomes in CHF,[43] it suggests that short-term TNFAIP3/NLRP3 levels might indirectly reflect underlying long-term risk.

Strengths and Limitations

The strengths of this study are as follows: First, the research design is rigorous. The diagnostic criteria were strictly determined based on the CHF management guidelines published by the ESC in 2023, with a concurrent non-CHF control group established. Second, the PSM method was employed to effectively control for confounding factors. After 1:1 matching, there were no statistical differences in variables between the CHF group and the non-CHF group except for TNFAIP3 and NLRP3, which ensures the reliability of the comparison results between the two groups. Third, the statistical analyses were diverse and in-depth, utilizing a comprehensive range of methods including multi-model logistic regression, RCS models, threshold effect analysis, and ROC curves. This allowed for a thorough analysis of the association between TNFAIP3, NLRP3, and the prognosis of patients with CHF, while also clarifying the threshold ranges and predictive efficacy differences between the two biomarkers, providing precise references for clinical risk stratification.

This study also has certain limitations. Firstly, it is designed as a single-center cohort study, and the sample size is limited. This may introduce selection bias, and caution is needed when extrapolating the results to CHF populations in other regions and different medical centers. The sample size lacked the statistical power to conduct a robust subgroup analysis.

Secondly, the follow-up period was only six months, which does not allow for the assessment of the long-term prognostic impact of TNFAIP3 and NLRP3 on patients with CHF (such as 1-year and 5-year survival rates). Thirdly, the retrospective data collection from medical records may introduce potential biases despite our focus on objective measures. Finally, MACEs were defined as a composite endpoint encompassing cardiac death, stroke, revascularization, and rehospitalization due to heart failure. We acknowledge that these events are not equivalent in clinical severity, particularly since cardiac death, as the hardest endpoint, may have different predictive factors compared to other events. In the present study, the limited number of cardiac death cases (n=11) precluded a separate analysis with sufficient statistical power. Rehospitalization for heart failure, constituting the most frequent component of the composite endpoint (43.5%), is itself a significant marker of disease progression, diminished quality of life, and increased healthcare burden. Consequently, despite the inherent heterogeneity, the use of a composite endpoint remains clinically valuable for identifying high-risk patient populations and providing signals for early intervention. Future studies with larger sample sizes are warranted to validate the predictive capacity of TNFAIP3 and NLRP3 specifically for the endpoint of cardiac death.

Future studies could advance in the following directions: first, conducting multicenter, large-sample size prospective cohort studies to broaden the sample source and extend the follow-up period, thereby verifying the generalizability and long-term effectiveness of the conclusions drawn from this study; second, combining tissue pathological testing with molecular biological experiments to clarify the expression characteristics and regulatory mechanisms of TNFAIP3 and NLRP3 in the myocardial tissues of patients with CHF, revealing their interactions; and third, exploring intervention strategies based on the targets of TNFAIP3 and NLRP3, such as pharmacologically regulating the activity of the NLRP3 or enhancing the expression levels of TNFAIP3, and observing their effects on cardiac function and prognosis in patients with CHF, thus providing new ideas and methods for the precision treatment of CHF.

Conclusion

This study demonstrated that serum levels of TNFAIP3 and NLRP3 were closely associated with both the progression and prognosis of CHF. Specifically, TNFAIP3 may serve as an independent protective factor against MACEs, whereas NLRP3 may act as an independent risk factor, exhibiting superior predictive capability for such events compared to TNFAIP3. The established thresholds for both biomarkers offer a quantifiable basis for clinical risk stratification in patients with CHF, which may enhance prognostic assessment and facilitate timely interventions.

Abbreviations

HF, Heart failure; ESC, European society of cardiology; TNFAIP3, Tumor necrosis factor alpha-induced protein 3; NLRP3, NOD-like receptor protein 3; CHF, Chronic heart failure; ELISA, Enzyme-linked immunosorbent assay; MACEs, Major adverse cardiovascular events; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; T2DM, Type 2 diabetes mellitus; WBC, White blood cells; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; FS, Fractional shortening; LVEF, Left ventricular ejection fraction; RCS, Restricted cubic spline; ROC, Receiver operating characteristic; CI, Confidence interval; AUROC, Area under the receiver operating characteristic.

Data Sharing Statement

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

Ethics Approval and Informed Consent

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Qingdao Municipal Hospital (approval number: 2024-KY-031). All participants provided written informed consent before participating in the study. This study adhered to the STROBE reporting guidelines.

Acknowledgments

We would like to thank the patients who participated in this study and the support from the Cardiology Department of Qingdao Municipal Hospital.

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Jun Guan: Project Administration, Resources, Writing - Review & Editing, Validation

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All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Qingdao Science & Technology for Public Well-being Project (Grant ID: 25-1-5-smjk-8-nsh).

Disclosure

The authors declare no conflicts of interest associated with this study.

References

1. McDonagh TA, Metra M, Adamo M, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726. doi:10.1093/eurheartj/ehab368
2. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2022;118(17):3272–3287. doi:10.1093/cvr/cvac013
3. Andreadou I, Ghigo A, Nikolaou PE, et al. Immunometabolism in heart failure. *Nat Rev Cardiol*. 2025;22(10):751–772. doi:10.1038/s41569-025-01165-8
4. Martens A, van Loo G. A20 at the crossroads of cell death, inflammation, and autoimmunity. *Cold Spring Harb Perspect Biol*.;121. doi:10.1101/cshperspect.a036418
5. Vereecke L, Beyaert R, van Loo G. The ubiquitin-editing enzyme A20 (TNFAIP3) is a central regulator of immunopathology. *Trends Immunol*. 2009;30(8):383–391. doi:10.1016/j.it.2009.05.007
6. Yamaguchi N, Yamaguchi N. The seventh zinc finger motif of A20 is required for the suppression of TNF-alpha-induced apoptosis. *FEBS Lett*. 2015;589(12):1369–1375. doi:10.1016/j.febslet.2015.04.022
7. Zheng C, Huang Y, Ye Z, et al. Infantile onset intractable inflammatory bowel disease due to novel heterozygous mutations in TNFAIP3 (A20). *Inflamm Bowel Dis*.;24(12):2613–2620. doi:10.1093/ibd/izy165
8. Zhang Q, Yu FX, Wu YL, et al. Novel gene therapy for rheumatoid arthritis with single local injection: adeno-associated virus-mediated delivery of A20/TNFAIP3. *Mil Med Res*.;9(1):34. doi:10.1186/s40779-022-00393-0
9. Cho MJ, Lee DG, Lee JW, et al. Endothelial PTP4A1 mitigates vascular inflammation via USF1/A20 axis-mediated NF-kappaB inactivation. *Cardiovasc Res*.;119(5):1265–1278. doi:10.1093/cvr/cvac193
10. Luo M, Wang X, Wu S, et al. A20 promotes colorectal cancer immune evasion by upregulating STC1 expression to block "eat-me" signal. *Signal Transduct Target Ther*.;8(1):312. doi:10.1038/s41392-023-01545-x
11. Fu J, Wu H. Structural mechanisms of NLRP3 inflammasome assembly and activation. *Annu Rev Immunol*. 41;301–316. doi:10.1146/annurev-immunol-081022-021207
12. Silvis MJM, Demkes EJ, Fiolet ATL, et al. Immunomodulation of the NLRP3 inflammasome in atherosclerosis, coronary artery disease, and acute myocardial infarction. *J Cardiovasc Transl Res*. 2021;14(1):23–34. doi:10.1007/s12265-020-10049-w
13. Ajoolabady A, Nattel S, Lip GYH, Ren J. Inflammasome signaling in atrial fibrillation: JACC State-of-the-Art review. *J Am Coll Cardiol*. 2022;79(23):2349–2366. doi:10.1016/j.jacc.2022.03.379
14. Higashikuni Y, Liu W, Numata G, et al. NLRP3 inflammasome activation through heart-brain interaction initiates cardiac inflammation and hypertrophy during pressure overload. *Circulation*.;147(4):338–355. doi:10.1161/CIRCULATIONAHA.122.060860
15. Hou L, Ye Y, Gou H, et al. A20 inhibits periodontal bone resorption and NLRP3-mediated M1 macrophage polarization. *Exp Cell Res*.;418(1):113264. doi:10.1016/j.yexcr.2022.113264
16. Al-Qazazi R, Lima PDA, Prisco SZ, et al. Macrophage-NLRP3 activation promotes right ventricle failure in pulmonary arterial hypertension. *Am J Respir Crit Care Med*.;206(5):608–624. doi:10.1164/rccm.202110-2274OC
17. Sano S, Oshima K, Wang Y, et al. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1beta/NLRP3 inflammasome. *J Am Coll Cardiol*.;71(8):875–886. doi:10.1016/j.jacc.2017.12.037

18. Voelkl J, Tuffaha R, Luong TTD, et al. Zinc inhibits phosphate-induced vascular calcification through TNFAIP3-mediated suppression of NF-kappaB. *J Am Soc Nephrol*. 2018;29(6):1636–1648. doi:10.1681/ASN.2017050492
19. Force M, McDonagh TA, Metra M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2024;26(1):5–17. doi:10.1002/ejhf.3024
20. Duan X, Hu M, Yang L, et al. IRG1 prevents excessive inflammatory responses and cardiac dysfunction after myocardial injury. *Biochem Pharmacol*. 2023;213:115614. doi:10.1016/j.bcp.2023.115614
21. Boulet J, Sridhar VS, Bouabdallaoui N, Tardif JC, White M. Inflammation in heart failure: pathophysiology and therapeutic strategies. *Inflamm Res*. 2024;73(5):709–723. doi:10.1007/s00011-023-01845-6
22. Grebe A, Hoss F, Latz E. NLRP3 inflammasome and the IL-1 pathway in atherosclerosis. *Circ Res*. 2018;122(12):1722–1740. doi:10.1161/CIRCRESAHA.118.311362
23. Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. *Nat Rev Immunol*. 2013;13(6):397–411. doi:10.1038/nri3452
24. Samoilova EV, Korotaeva AA, Zhirov IV, et al. Interleukin 6 signalling in heart failure with preserved and reduced ejection fraction. *Kardiologiia*. 64(3):34–39. doi:10.18087/cardio.2024.3.n2534
25. Fontes JA, Rose NR, Cihakova D. The varying faces of IL-6: from cardiac protection to cardiac failure. *Cytokine*. 2015;74(1):62–68. doi:10.1016/j.cyto.2014.12.024
26. Verstrepen L, Verhelst K, van Loo G, Carpentier I, Ley SC, Beyaert R. Expression, biological activities and mechanisms of action of A20 (TNFAIP3). *Biochem Pharmacol*. 2010;80(12):2009–2020. doi:10.1016/j.bcp.2010.06.044
27. Wertz I, Dixit V. A20–a bipartite ubiquitin editing enzyme with immunoregulatory potential. *Adv Exp Med Biol*. 2014;809:1–12. doi:10.1007/978-1-4939-0398-6_1
28. Mooney EC, Sahingur SE. The ubiquitin system and A20: implications in health and disease. *J Dent Res*. 2021;100(1):10–20. doi:10.1177/0022034520949486
29. Priem D, van Loo G, Bertrand MJM. A20 and cell death-driven inflammation. *Trends Immunol*. 2020;41(5):421–435. doi:10.1016/j.it.2020.03.001
30. Catrysse L, Vereecke L, Beyaert R, van Loo G. A20 in inflammation and autoimmunity. *Trends Immunol*. 2014;35(1):22–31. doi:10.1016/j.it.2013.10.005
31. Zhang R, Xu L, Zhang D, et al. Cardioprotection of ginkgolide B on myocardial ischemia/reperfusion-induced inflammatory injury via regulation of A20-NF-kappaB pathway. *Front Immunol*. 2018;9:2844. doi:10.3389/fimmu.2018.02844
32. Shaw J, Eydelnant IA, Kirshenbaum LA. Transgenic expression of A20 prevents cardiac cell death and myocardial dysfunction after myocardial infarction. *Circulation*. 2007;115(14):1827–1829. doi:10.1161/CIRCULATIONAHA.106.687475
33. Patel VI, Daniel S, Longo CR, et al. A20, a modulator of smooth muscle cell proliferation and apoptosis, prevents and induces regression of neointimal hyperplasia. *FASEB J*. 2006;20(9):1418–1430. doi:10.1096/fj.05-4981com
34. Shi H, Yu Y, Li D, et al. TNIP3 protects against pathological cardiac hypertrophy by stabilizing STAT1. *Cell Death Dis*.;15(6):450. doi:10.1038/s41419-024-06805-4
35. Zhang X, Qu H, Yang T, Kong X, Zhou H. Regulation and functions of NLRP3 inflammasome in cardiac fibrosis: current knowledge and clinical significance. *Biomed Pharmacother*. 2021;143:112219. doi:10.1016/j.biopha.2021.112219
36. Deng Y, Liu X, Xie M, et al. Obesity enables NLRP3 activation and induces myocardial fibrosis via hyperacetylation of HADHa. *Diabetes*.;72(11):1597–1608. doi:10.2337/db23-0264
37. Zeng C, Duan F, Hu J, et al. NLRP3 inflammasome-mediated pyroptosis contributes to the pathogenesis of non-ischemic dilated cardiomyopathy. *Redox Biol*. 2020;34:101523. doi:10.1016/j.redox.2020.101523
38. Alogna A, Koepp KE, Sabbah M, et al. Interleukin-6 in patients with heart failure and preserved ejection fraction. *JACC Heart Fail*. 2023;11(11):1549–1561. doi:10.1016/j.jchf.2023.06.031
39. Berger M, Marz W, Niessner A, et al. IL-6 and hsCRP predict cardiovascular mortality in patients with heart failure with preserved ejection fraction. *ESC Heart Fail*. 2024;11(6):3607–3615. doi:10.1002/ehf2.14959
40. Abbate A, Toldo S, Marchetti C, Kron J, Van Tassell BW, Dinarello CA. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. *Circ Res*. 2020;126(9):1260–1280. doi:10.1161/CIRCRESAHA.120.315937
41. Tan W, Cheng S, Qiu Q, et al. Celastrol exerts antiarrhythmic effects in chronic heart failure via NLRP3/Caspase-1/IL-1beta signaling pathway. *Biomed Pharmacother*. 2024;177:117121. doi:10.1016/j.biopha.2024.117121
42. Yang H, Shen X, Wang H, Shuai W. Tumour necrosis factor alpha-induced protein 3-interacting protein 3 overexpression protects against arrhythmogenic remodelling in the heart failure mice. *Europace*.;271. doi:10.1093/europace/euaf002
43. Dai Y, Yang J, Takagi A, et al. In-hospital and long-term outcomes of congestive heart failure: predictive value of B-type and amino-terminal pro-B-type natriuretic peptides and their ratio. *Exp Ther Med*. 2017;14(2):1715–1721. doi:10.3892/etm.2017.4686