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The effect of NLRP3 inflammasome on cardiovascular prognosis in patients with acute coronary syndrome

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The NOD-like receptor protein domain associated protein 3 (NLRP3) inflammasome is critical in inflammatory responses and may be a valuable prognostic biomarker in acute coronary syndrome (ACS). We aimed to investigate the association between NLRP3 inflammasome levels and short-term outcomes in patients with ACS. We enrolled 295 patients with ACS who were monitored for 6 months for major adverse cardiovascular events (MACEs). The NLRP3 inflammasome was quantified using enzyme-linked immunosorbent assays, with the Gensini score used to assess disease severity. A Cox regression model evaluated whether NLRP3 inflammasome levels were independent predictors of MACEs. Spearman correlation analysis demonstrated a significant positive correlation between NLRP3 inflammasome levels and the Gensini score ($r = 0.55$, $p < 0.001$). Plasma NLRP3 inflammasome levels were significantly higher in the MACEs group (8.48 ng/mL) compared with the no-MACEs group (3.48 ng/mL) ($p < 0.001$). Multivariate Cox regression identified NLRP3 inflammasome content as an independent risk factor for MACEs (hazard ratio 1.104, $p = 0.001$; area under the curve: 0.780 [95% confidence interval 0.721–0.840], $p < 0.001$). Elevated plasma NLRP3 inflammasome levels correlated with ACS severity and were associated with poorer short-term outcomes in patients with ACS.

Keywords Acute coronary syndrome, NLRP3 inflammasome, Short-term prognosis

Acute coronary syndrome (ACS) results from the rupture of atherosclerotic plaque and the subsequent formation of a thrombus, leading to myocardial ischemia and necrosis[1]. Owing to its high morbidity, disability, and mortality rates worldwide, ACS imposes significant economic burdens on many countries[2]. Percutaneous coronary intervention (PCI) is recommended as the primary method for treating patients with acute myocardial infarction (AMI) owing to its advantages, such as minimal trauma and rapid postoperative recovery[3]. However, substantial improvements in the prognosis of patients with AMI have not been observed, and adverse events such as heart failure and stroke continue to occur post-PCI[4,5]. Therefore, biomarkers are needed that can facilitate the prediction of major adverse cardiovascular events (MACEs) in patients with ACS. The development of ACS is not solely attributable to lipid metabolism disorders, and inflammation is known to play a crucial role[6]. Thus, anti-inflammatory and immune regulation strategies have emerged as new approaches for ACS treatment[6].

The NOD-like receptor protein domain associated protein 3 (NLRP3) inflammasome is a well-known inflammasome composed of NLRP3, pro-caspase-1, and apoptosis-associated spot-like protein[7]. The NLRP3 inflammasome plays a crucial role in the innate immune system through initiating the activation of downstream caspase-1 and the release of pro-inflammatory cytokines interleukin (IL)-1β and IL-18 in response to microbial attacks and cellular injury[8]. It is a vital guardian of the innate immune system, detecting threats to the host by recognizing specific molecules such as pathogen- or damage-associated molecular patterns and disruptions in cellular homeostasis, referred to as homeostasis-altering molecular processes or effector-triggered immunity[9].

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The NLRP3 inflammasome has been extensively investigated in a variety of inflammation-related diseases, including inflammatory bowel disease, asthma, and rheumatoid arthritis[10–12]. In recent years, the NLRP3 inflammasome has been reported to have an important role in cardiovascular diseases, especially coronary atherosclerotic diseases[13,14].The NLRP3 inflammasome, which is found in monocytes and neutrophils, is activated by cholesterol crystals present in atherosclerotic lesions[14,15]. When activated, the NLRP3 inflammasome stimulates the release of inflammatory cytokines such as IL-1β and IL-18, contributing to plaque development and increased cardiac vulnerability[8]. Moreover, the NLRP3 inflammasome can exacerbate myocardial ischemic injury and ventricular remodeling[16–18]. Given its role in coronary atherosclerosis, the NLRP3 inflammasome may serve as a potential biomarker of prognosis in patients with ACS.

Early identification of high-risk groups among patients with ACS and early intervention can improve patient prognosis and reduce individual as well as societal economic stress. However, few clinical studies have investigated the NLRP3 inflammasome as a potential prognostic biomarker in patients with ACS. This prospective study aimed to investigate the association between NLRP3 inflammasome levels and disease severity and prognosis in patients with ACS.

Patients and methods

Study design and population

Patients diagnosed with ACS who underwent coronary arteriography and/or PCI from June 2021 to March 2022 in Liaocheng People's Hospital were included in the study ($n=295$). Participants were divided into two groups based on the median plasma NLRP3 inflammasome content. We investigated the association between the NLRP3 inflammasome content and the number of diseased coronary vessels. The Gensini score was used to further determine the association between the NLRP3 inflammasome and disease severity in patients with ACS[19]. Moreover, we aimed to determine whether NLRP3 inflammasome levels could serve as a predictor of MACEs. The diagnosis of ACS was based on established guidelines[20,21]. The exclusion criteria comprised patients with various types of infections, immune system diseases, inflammatory bowel disease, tumors, stroke, arrhythmia, liver and kidney insufficiency, and heart failure. The research process is shown in Fig. 1. This study was approved by the Medical Ethics Committee of Liaocheng People's Hospital (approval number: 2021096) and strictly adhered to the Declaration of Helsinki. Written informed consent was obtained from all patients.

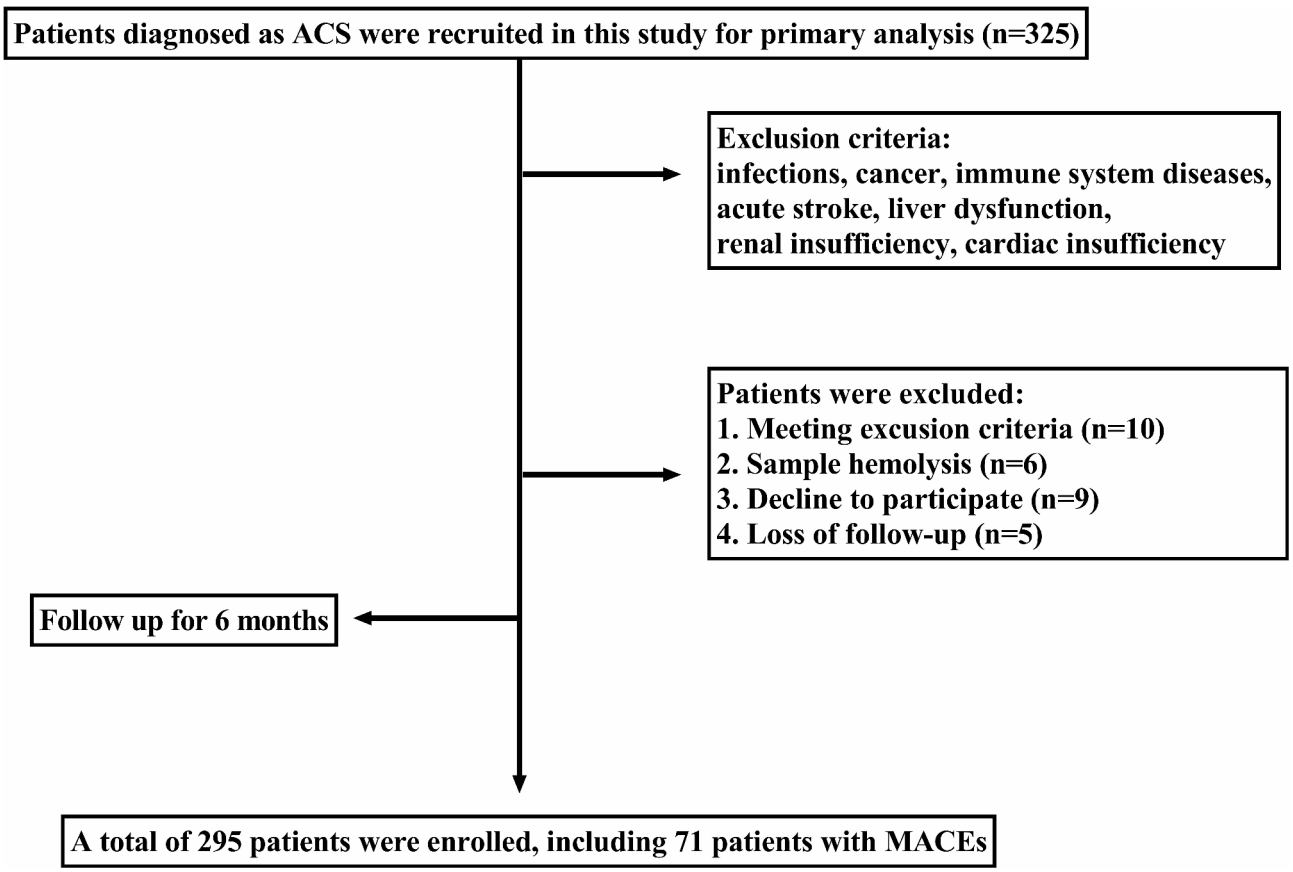

Fig. 1. The flowchart of the studied patients. We strictly followed the flowchart. Ultimately, 295 people were included in the statistical analysis, and 71 patients developed MACEs. *ACS* acute coronary syndrome, *MACEs* major adverse cardiovascular events.

Data collection

Data were obtained from laboratory tests conducted upon admission. Patient characteristics in relation to sex, age, hypertension, smoking status, type 2 diabetes (T2DM), blood pressure, and heart rate were recorded. Hematological indicators comprised the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, red blood cell distribution width, eosinophils, platelet distribution width, white blood cell count (WBC), hemoglobin, C-reactive protein (CRP), cardiac troponin I (cTnI), type B natriuretic peptide (BNP), low-density lipoprotein, D-dimer, high-density lipoprotein, and creatinine (Cr) levels. Imaging data included measurements such as left ventricular end-diastolic dimension, left ventricular ejection fraction (LVEF), and the presence of coronary artery lesions (left anterior descending, right coronary artery, and left circumflex).

Detection of plasma NLRP3 inflammasome expression

Prior to the administration of any medications, 5 mL venous blood samples were collected from the study participants for evaluation. Blood samples were collected using tubes containing ethylenediaminetetraacetic acid. The samples were promptly centrifuged at 1000×g for 15 min. After plasma separation, the plasma was stored at -80 °C until use. NLRP3 inflammasome content in the plasma was assessed using an enzyme-linked immunosorbent assay (ELISA). The manufacturer's instructions (Ml560903-2, Mlbio, Shanghai, China) were strictly followed to determine the plasma NLRP3 inflammasome content.

Follow-up of patients for MACEs

Patient follow-up was conducted collectively by three doctors. In the event of MACEs occurring, follow-up was terminated within 6 months. Outcomes considered as part of the MACEs included cardiac death, stroke, revascularization, new-onset heart failure (based on Framingham criteria)[22], and readmission owing to ACS. Cardiac death was defined as death caused by cardiac-related factors, excluding deaths resulting from other causes. Shock was diagnosed based on a systolic blood pressure (SBP) of <90 mmHg, with consideration given to excluding other types of shock. Revascularization included both PCI and coronary artery bypass grafting. Heart failure referred to the clinical symptoms of breathlessness and pulmonary congestion[22]. Readmission was defined as the admission of a patient to hospital owing to cardiac causes such as angina and myocardial infarction.

Statistical analysis

Statistical analysis was performed using SPSS (version 23.0; IBM, Armonk, NY, USA) and MedCalc statistical (version 20.215; MedCalc, Ostend, Belgium) software. Non-normally distributed data are presented as the median (interquartile range). Comparisons between non-normally distributed groups were conducted using Mann–Whitney U and Kruskal–Wallis H tests. Categorical variables were analyzed using frequency (percentage) and compared using a chi-square test. Spearman's correlation analysis was performed to analyze the correlation between variables. A Cox regression model was applied to determine the independent risk factors for MACEs. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive power of the NLRP3 inflammasome, with DeLong's test used to compare the area under the curves (AUCs). Survival analysis was conducted using a Kaplan–Meier curve. All tests were two-sided, and a significance level of $p<0.05$ was considered statistically significant.

Results

Patient characteristics

In total, 295 study patients were included. Based on the median level of the NLRP3 content, participants were divided into two groups, namely, an NLRP3 $\leq$ 3.98 ng/mL ($n=148$) group and an NLRP3 $>$ 3.98 ng/mL ($n=147$) group. Table 1 shows the characteristics of the two patient groups. No significant differences were observed between the two groups in terms of sex, smoking status, hypertension, T2DM, and heart rate. However, significant differences were observed in terms of age, SBP, diastolic blood pressure, and NLR, eosinophil, WBC, D-dimer, cTnI, CRP, BNP, Cr, and LVEF levels ($p<0.05$).

NLRP3 levels and the number of diseased coronary vessels

We assessed the number of diseased major coronary vessels in the patients and categorized them into three groups for comparison. The content of the NLRP3 inflammasome exhibited variations among the three groups (Table 2). The NLRP3 inflammasome content increased with the number of coronary lesions: one vessel (3.55 ng/mL), two vessels (3.86 ng/mL), and three vessels (4.62 ng/mL) ($p<0.05$). Spearman's correlation analysis showed a positive correlation between NLRP3 and the Gensini score ($r=0.55$, $p<0.001$; Fig. 2).

Characteristics of the MACEs and no-MACEs groups

In total, 295 patients were followed up for a duration of 1–6 months. Of these, 71 patients experienced MACEs (cardiac death [$n=11$], stroke [$n=10$], revascularization [$n=10$], congestive heart failure [$n=16$], and readmission [$n=24$]). A comparison between patients with MACEs and those without MACEs is presented in Table 3. Patients who experienced MACEs were found to be older and had a higher heart rate. Additionally, the MACEs group displayed higher levels of NLR, WBC, D-dimer, CRP, BNP, and cTnI, while their LVEF levels were lower ($p<0.05$). The plasma NLRP3 content in the MACEs group was significantly higher compared with that of the no-MACEs group (8.48 vs. 3.48 ng/mL, $p<0.001$).

Risk factors for MACEs

Cox regression analysis identified risk factors associated with MACEs (Table 4). In the univariate model, age, heart rate, Gensini score, and NLRP3, NLR, WBC, CRP, cTnI, BNP, and LVEF levels were independent predictors

Variable	All patients ($n=295$)	NLRP3 ≤ 3.98 ng/mL ($n=148$)	NLRP3 > 3.98 ng/mL ($n=147$)	p-value
Age (year)	65(24)	63(16)	67(17)	0.014
Male n (%)	196(66.4)	105(70.1)	91(61.9)	0.508
Smoking n (%)	123(41.7)	65(44.0)	58(39.5)	0.852
Hypertension n (%)	192(65.1)	101(68.2)	91(61.9)	0.851
T2DM n (%)	90(30.5)	48(32.4)	42(28.6)	0.797
Heart rate (bpm)	78(17)	76(17)	78(18)	0.052
SBP (mmHg)	132(27)	135(26)	130(33)	0.044
DBP (mmHg)	78(16)	80(15)	75(18)	0.001
Laboratory findings				
NLR	3.23(3.97)	2.94(2.88)	3.48(5.20)	0.026
PLR	144.67(86.54)	140.41(75.23)	148.45(94.62)	0.285
RDW (fL)	43.10(4.20)	42.75(3.95)	43.30(4.65)	0.433
PDW (fL)	11.80(4.90)	11.90(4.90)	11.80(5.10)	0.941
Eosinophils ($\times10^9$/L)	0.07(0.12)	0.08(0.13)	0.06(0.10)	0.020
Hb (g/L)	135(25)	137(22)	134(29)	0.066
WBC count ($\times10^9$/L)	7.80(3.86)	7.39(3.39)	8.11(4.75)	0.005
CRP (mg/L)	2.07(4.99)	1.56(3.58)	3.15(10.04)	<0.001
D-Dimer (ng/mL)	0.34(0.53)	0.30(0.40)	0.44(0.66)	0.003
cTnI (ng/mL)	0.45(4.49)	0.14(3.24)	0.75(6.39)	0.007
BNP (pg/mL)	356(1507)	168(811)	617(2254)	< 0.001
LDL (mmol/L)	2.65(1.13)	2.68(1.23)	2.65(1.07)	0.981
HDL (mmol/L)	1.09(0.36)	1.11(0.39)	1.06(0.26)	0.201
Cr (mmol/L)	71.8(22.7)	69.9(21.7)	74.5(25.5)	0.045
LVEDD (mm)	46(6)	45(5)	46(6)	0.386
LVEF (%)	57(17)	59(14)	52(19)	0.001
MACEs n (%)	71(0.24)	16(10.81)	55(37.41)	< 0.001

Table 1. Patients' characteristics based on median of NLRP3 levels. *T2DM* type 2 diabetes mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *RDW* red blood cell distribution width, *PDW* platelet distribution width, *Hb* hemoglobin, *WBC* white blood cell, *CRP* C-reactive protein, *cTnI* cardiac Troponin I, *BNP* type B natriuretic peptide, *LDL*, low-density lipoprotein cholestero, *HDL* high-density lipoprotein cholestero, *Cr* creatinine, *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricle ejection fraction, *MACEs* major adverse cardiovascular events.

No. of vessels	NLRP3 (ng/mL)
One vessel	3.55 (2.43)
Two vessels	3.86 (4.25)*
Three vessels	4.62 (8.89)*#

Table 2. NLRP3 levels according to the number of diseased vessels. *$p < 0.05$ in comparison to one vessel. #$p < 0.05$ in comparison to two vessels.

of MACEs. However, in the multivariate Cox regression model, only the Gensini score (hazard ratio [HR] 1.012, $p=0.027$), NLRP3 (HR 1.104, $p=0.001$), CRP (HR 1.024, $p=0.007$), and LVEF (HR 0.937, $p=0.001$) remained as independent predictors of MACEs.

Survival analysis

Survival analysis findings using Kaplan–Meier curves are shown in Fig. 3. The Kaplan–Meier curves were generated based on the median NLRP3 content (3.98 ng/mL). The results indicated a significantly poorer cumulative outcome in the high-risk group (log-rank test: chi-square 34.195, $p<0.001$).

ROC curve analysis

ROC curves were generated to evaluate the potential predictive power of three biomarkers, namely, CRP, LVEF, and NLRP3, for MACEs (Fig. 4). The cutoff values for CRP, LVEF, and NLRP3 were 3.625 mg/L, 44%, and 5.391 ng/mL, respectively (sensitivity: 63.4%, 88.8%, and 67.6%, respectively, specificity: 70.5%, 42.3%, and 76.3%,

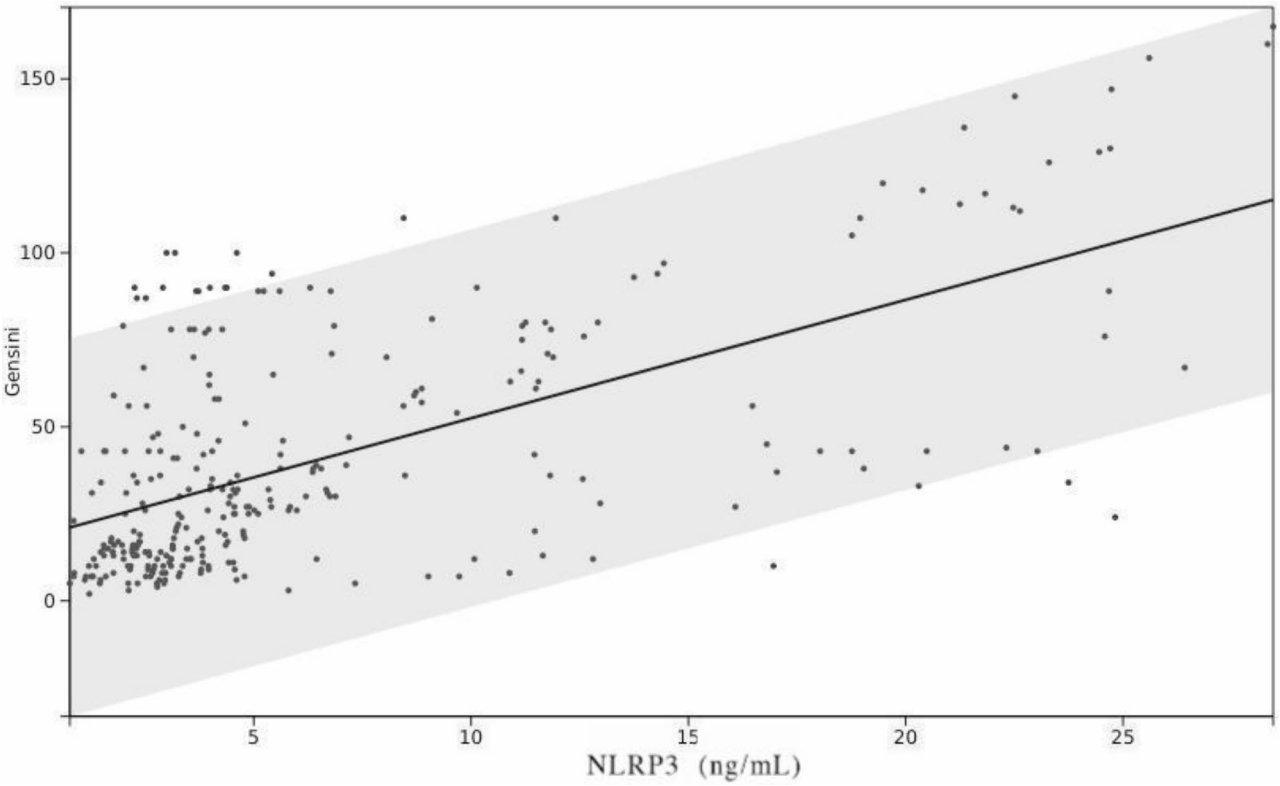

Fig. 2. Spearman correlation analysis was used to assess the correlation between Gensini score and NLRP3 content. Spearman correlation analysis revealed a positive correlation between NLRP3 and the Gensini score ($r = 0.55$, $p < 0.001$).

respectively) (Table 5). DeLong's test was used to determine the AUCs of the three ROC curves (Table 6). The results showed that NLRP3 had a significantly higher predictive power than CRP (0.780 vs. 0.700, $p = 0.043$).

Discussion

The poor prognosis in patients with ACS is a critical issue that needs to be addressed. Early identification of high-risk groups among patients with ACS, which can improve patient prognosis and reduce the patient and economic burden, requires a variety of approaches such as health education, enhanced follow-up, and drug treatment. This study aimed to investigate the association between NLRP3 inflammasome levels and disease severity in patients with ACS and the predictive ability of NLRP3 inflammasome levels for MACEs in this population. We undertook a prospective study of 295 patients with ACS. We measured plasma NLRP3 inflammasome levels, assigned Gensini scores, and performed a 6-month follow-up to record MACEs. Finally, we observed that NLRP3 inflammasome levels correlated with disease severity and prognosis in patients with ACS.

Involvement of the NLRP3 inflammasome in coronary atherosclerosis was first reported by Duewell et al. in 2010[23]. Subsequent studies by Afrasyab et al.[24] and Zhu et al.[25] confirmed the positive correlation between NLRP3 levels and coronary atherosclerosis severity, as well as the increased NLRP3 content in peripheral blood monocytes in ACS. Furthermore, Zhu et al. reported that rosuvastatin can decelerate the atherosclerosis process through down-regulating NLRP3. These findings collectively highlight the important role of the NLRP3 inflammasome in atherosclerosis. The precise mechanisms by which NLRP3 is involved in atherosclerosis are not fully understood; however, they may involve endothelial dysfunction, oxidative stress, and inflammatory responses. The NLRP3 inflammasome plays a crucial role in endothelial dysfunction across various cardiovascular conditions. Activation of NLRP3 contributes to endothelial dysfunction in angiotensin II-induced hypertension through reducing endothelial nitric oxide synthase phosphorylation and increasing IL-1β levels[26]. During hypercholesterolemia, endothelial NLRP3 activation directly impairs endothelial function through increased caspase-1 activity and High mobility group box 1 protein expression[27]. A recent study reported that a combination of idebenone and rosuvastatin effectively prevented atherosclerosis through inhibition of oxidative stress and NLRP3 inflammasome activation[28]. The NLRP3 inflammasome is a cytoplasmic complex that activates in response to cellular perturbations, leading to the production of pro-inflammatory cytokines IL-1β and IL-18[29]. IL-18 plays a significant role in the development and progression of atherosclerosis[30]. IL-18 is highly expressed in atherosclerotic plaques, particularly in macrophages, and its levels are significantly higher in unstable plaques compared with stable ones[31]. In conclusion, the NLRP3 inflammasome promotes ACS disease progression, which provides theoretical support for our findings.

Variable	ACS ($n=295$)	MACEs ($n=71$)	No MACEs ($n=224$)	p-value
Age (year)	65(24)	68(16)	63(15)	0.014
Male n (%)	196(66.4)	45(63.4)	151(67.4)	0.531
Smoking n (%)	123(41.7)	25(39.4)	98(43.8)	0.204
Hypertension n (%)	192(65.1)	40(56.3)	152(67.9)	0.076
T2DM n (%)	90(30.5)	21(29.6)	69(30.8)	0.845
Heart rate (bpm)	78(17)	82(22)	77(15)	0.010
SBP (mmHg)	132(27)	127(38)	133(26)	0.051
DBP (mmHg)	78(16)	76(21)	79(16)	0.123
Laboratory findings				
NLRP3 (ng/mL)	3.98(4.75)	8.48(14.57)	3.48 (2.86)	<0.001
NLR	3.23(3.97)	3.82(5.47)	2.96(3.20)	0.001
PLR	144.67(86.54)	148.45(116.31)	144.53(76.67)	0.404
RDW (fL)	43.10(4.20)	43.50(5.00)	42.90(4.00)	0.202
PDW (fL)	11.80(4.90)	11.80(4.80)	11.80(5.10)	0.704
Eosinophils ($\times10^9$/L)	0.07(0.12)	0.05(0.13)	0.07(0.11)	0.127
Hb (g/L)	135(25)	132(30)	136(23)	0.076
WBC count ($\times10^9$/L)	7.80(3.86)	8.82(5.02)	7.61(3.44)	0.001
CRP (mg/L)	2.07(4.99)	5.22(17.19)	1.77(3.70)	<0.001
D-Dimer (ng/mL)	0.34(0.53)	0.49(0.57)	0.31(0.48)	0.001
cTnI (ng/mL)	0.45(4.49)	1.70(10.75)	0.16(3.69)	<0.001
BNP (pg/mL)	356(1507)	976(2405)	198(861)	<0.001
LDL (mmol/L)	2.65(0.68)	2.74(1.37)	2.65(1.07)	0.448
HDL (mmol/L)	1.09(0.36)	1.05(0.43)	1.10(0.34)	0.428
Cr (mmol/L)	71.8(22.7)	72.20(24.0)	71.45(22.4)	0.495
LVEDD (mm)	46(6)	46(6)	45(6)	0.230
LVEF (%)	57(17)	44(19)	59(14)	<0.001

Table 3. The characteristics of MACEs and no MACEs groups. *ACS* acute coronary syndrome, *MACEs* major adverse cardiovascular events, *T2DM* type 2 diabetes mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *RDW* red blood cell distribution width, *PDW* platelet distribution width, *Hb* hemoglobin, *WBC* white blood cell, *CRP* C-reactive protein, *cTnI* cardiac Troponin I, *BNP* type B natriuretic peptide, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *Cr* creatinine, *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricle ejection fraction.

The NLRP3 inflammasome can therefore be used to predict prognosis in patients with ACS, which is consistent with the results of two previous studies[24,25]. However, differences in our study were that we expanded the included sample to include 295 patients with ACS, whereas Afrasyab et al. only included 93 patients with ACS. Moreover, we assayed NLRP3 inflammasome in different samples. Afrasyab et al. and Zhu et al. tested for NLRP3 inflammasome in peripheral blood mononuclear cells, whereas we tested for NLRP3 inflammasome in plasma. Despite these differences in research methods, our results corroborate previous findings. We also examined the expression of various inflammatory indicators, including WBC, NLR, CRP, and NLRP3, in patients with ACS and assessed their effect on prognosis. Our findings indicated that both CRP and NLRP3 act as independent predictors of MACEs. An elevated WBC count has been reported to be associated with MACEs[32,33], and our findings provided further support for this association, as the MACEs group exhibited higher WBC count levels than those in the no-MACEs group. While NLR has been identified as a prognostic indicator of MACEs in AMI[34], our multivariate Cox regression analysis did not confirm this as an independent predictor in patients with ACS. These differences may be attributable to the limited sample size and the need for larger studies in future. CRP, a well-established inflammatory indicator and commonly used to monitor the inflammatory response in clinical practice, is involved in the development of atherosclerosis and thrombosis through various mechanisms[35]. Previous studies have shown an association between elevated CRP levels and long-term prognosis. In a cohort study of 199 patients with ACS and involving a 3-year follow-up, a high CRP group had an odds ratio of 7.41 for MACEs[36]. Furthermore, the CRP/albumin ratio has been shown to serve as an accessible biomarker for assessing the risk of stent restenosis in patients with ST-segment elevation myocardial infarction[37]. Our findings support the association between high CRP levels and poor short-term outcomes in ACS. In addition, we compared the NLRP3 inflammasome and CRP using ROC curves and concluded that the NLRP3 inflammasome had a stronger predictive ability.

This study presents several innovative findings. We identified a correlation between the NLRP3 inflammasome and the severity of disease in patients with ACS. Moreover, NLRP3 inflammasome levels were found to be associated with short-term prognosis in patients with ACS, thereby addressing a significant gap in current

Variable	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.023(1.002–1.044)	0.035	1.024(0.994–1.055)	0.113
Male	0.837(0.479–1.462)	0.531		
Smoking	1.431(0.822–2.490)	0.205		
Hypertension	1.636(0.947–2.826)	0.077		
T2DM	1.060(0.591–1.899)	0.845		
Heart rate	1.023(1.008–1.038)	0.002	1.013(0.988–1.038)	0.311
SBP	0.985(0.973–0.997)	0.082		
DBP	0.983(0.963–1.003)	0.104		
Gensini	1.025(1.016–1.033)	<0.001	1.012(1.001–1.023)	0.027
NLRP3	1.098(1.069–1.127)	<0.001	1.104(1.042–1.170)	0.001
NLR	1.073(1.032–1.116)	<0.001	0.968(0.866–1.082)	0.569
PLR	1.003(1.000-1.006)	0.053		
RDW	1.030(0.977–1.087)	0.271		
PDW	0.968(0.876–1.071)	0.529		
Eosinophils	0.978(0.119–8.055)	0.984		
Hb	0.988(0.974–1.002)	0.087		
WBC	1.109(1.054–1.167)	<0.001	0.998(0.882–1.129)	0.977
CRP	1.014(1.008–1.020)	<0.001	1.024(1.006–1.041)	0.007
D-Dimer	1.146(0.0944-1.392)	0.168		
cTnI	1.036(1.011–1.061)	0.004	1.021(0.973–1.071)	0.397
BNP	1.000(1.000–1.000)	0.001	1.000(1.000–1.000)	0.583
LDL	1.263(0.931–1.714)	0.134		
HDL	1.275(0.562–2.890)	0.561		
Cr	1.006(0.998–1.013)	0.138		
LVEDD	1.014(0.970–1.060)	0.543		
LVEF	0.947(0.929–0.965)	<0.001	0.937(0.902–0.973)	0.001

Table 4. Univariate and multivariate COX regression for predictors of MACEs. *MACEs* major adverse cardiovascular events, *T2DM* type 2 diabetes mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *RDW* red blood cell distribution width, *PDW* platelet distribution width, *Hb* hemoglobin, *WBC* white blood cell, *CRP* C-reactive protein, *cTnI* cardiac Troponin I, *BNP* type B natriuretic peptide, *LDL* low-density lipoprotein cholestero, *HDL* high-density lipoprotein cholesterol, *Cr* creatinine, *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricle ejection fraction, *HR* hazard ratio, *CI* confidence interval.

research. Furthermore, our research holds significant implications for identifying high-risk populations among patients with ACS for early intervention, thereby improving prognosis. Additionally, it provides new therapeutic strategies for targeted treatment of ACS through the modulation of inflammatory factors, specifically the NLRP3 inflammasome.

While well-designed, our study had some limitations. It was a single-center, small-sample, prospective study. We only examined the effect of the NLRP3 inflammasome on the short-term prognosis of patients with ACS. Additionally, plasma NLRP3 inflammasome levels were only measured in hospitalized patients on admission, and no dynamic monitoring was conducted. Furthermore, we did not compare the association between the NLRP3 inflammasome and other prognostic scores, such as the Thrombolysis in Myocardial Infarction score[38] and the Hemoglobin, Albumin, Lymphocyte, Platelet score[39].

Researchers need to investigate inflammatory immunity in relation to cardiovascular disease in greater depth. Although it has been demonstrated that the NLRP3 inflammasome is associated with prognosis in patients with ACS, multicenter studies with larger samples are needed for further confirmation. In addition, the NLRP3 inflammasome is an important therapeutic target. Several inhibitors of the NLRP3 inflammasome are currently being investigated in clinical trials[40,41]. We anticipate the development of further anti-inflammatory drugs for clinical use.

Conclusions

NLRP3 inflammasome content in plasma was found to be associated with the severity of ACS, with high plasma NLRP3 inflammasome content linked to a poor short-term prognosis in ACS.

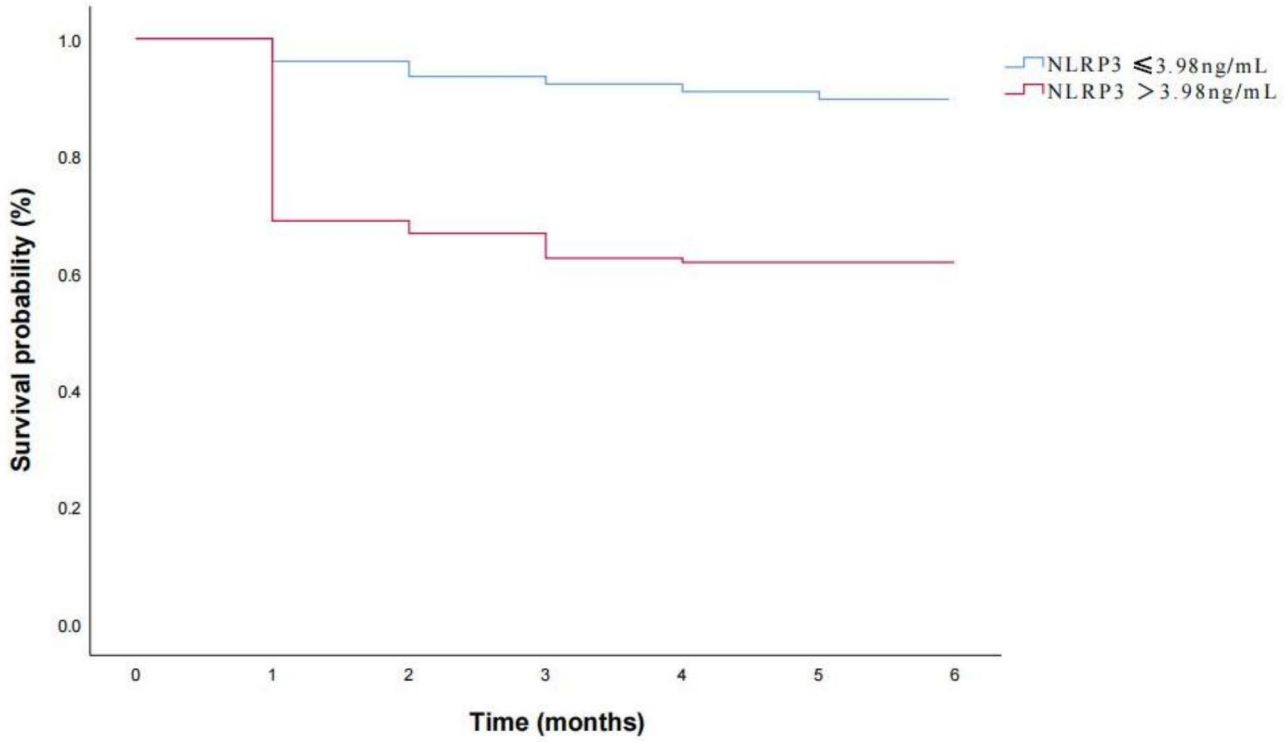

Fig. 3. Kaplan–Meier analysis for cumulative MACEs based on NLRP3 levels. The results indicated a significantly poorer cumulative outcome in the high-risk group (Log-rank test: Chi-Square = 34.195, $p < 0.001$).

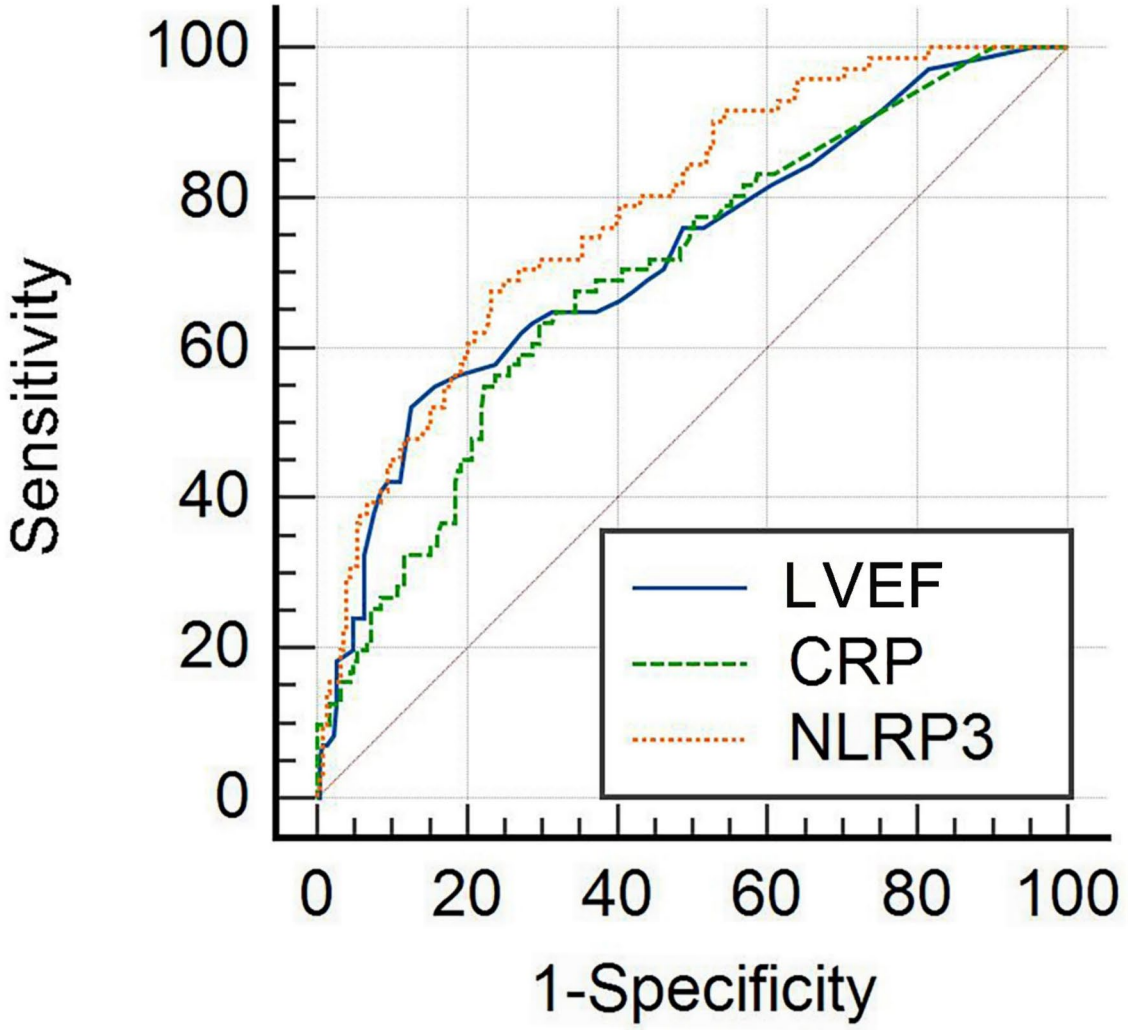

Fig. 4. Receiver operating characteristic curves for MACEs in ACS patients. ROC curves were generated to evaluate the potential predictive power of three biomarkers, namely, CRP, LVEF, and NLRP3, for MACEs. The cutoff values for CRP, LVEF, and NLRP3 were 3.625 mg/L, 44%, and 5.391 ng/mL, respectively (sensitivity: 63.4%, 88.8%, and 67.6%, respectively, specificity: 70.5%, 42.3%, and 76.3%, respectively). *CRP* C-reactive protein, *LVEF* left ventricle ejection fraction, *MACEs* major adverse cardiovascular events.

	AUC	95% CI	*p*-value	Sensitivity	Specificity	Cut-off
NLRP3	0.780	0.721–0.840	<0.001	67.6%	76.3%	5.391 (ng/mL)
CRP	0.700	0.631–0.769	<0.001	63.4%	70.5%	3.625 (mg/L)
LVEF	0.723	0.652–0.793	<0.001	88.8%	42.3%	44%

Table 5. The performances of NLRP3, CRP, and LVEF in patients with ACS. *CRP* C-reactive protein, *LVEF* left ventricle ejection fraction, *AUC* area under curve, *CI* confidence interval.

	Difference of AUC	Standard error	95% CI	z-value	*p*-value
NLRP3 vs. CRP	0.080	0.040	0.003 to 0.161	2.027	0.043
NLRP3 vs. LVEF	0.057	0.046	− 0.031 to 0.148	1.289	0.198
CRP vs. LVEF	0.023	0.047	− 0.068 to 0.115	0.496	0.620

Table 6. Paired comparison of ROC curves (DeLong's test). *CRP* C-reactive protein, *LVEF* left ventricle ejection fraction, *AUC* area under curve, *CI* confidence interval.

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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Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Medical Ethics Committee of Liaocheng People's Hospital with the approval number: 2021096, dated January 2021. All participants provided written informed consent to participate in the study and for their data to be published. The work described has been carried out in accordance with the Code of Ethics of the World Medical Association Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

Additional information

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