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Correlation between Plasma Nucleolin and Coronary Plaque Stability and Lesion Severity in Acute Coronary Syndrome: Postprint

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Abstract

背景 Acute coronary syndrome (ACS) is a pathological clinical syndrome characterized by rupture or erosion of atherosclerotic plaques in coronary arteries, with subsequent complete or incomplete occlusive thrombus formation. The selection of specific and sensitive serological markers and detection methods for rapid and accurate early diagnosis, condition assessment, and therapeutic intervention in ACS patients holds significant clinical value.

目的 To investigate the relationship between plasma nucleolin (NCL) levels and coronary plaque stability and lesion severity in ACS patients, as well as the predictive value of NCL for ACS.

方法 A total of 117 patients hospitalized in the Department of Cardiology at Changsha First Hospital in 2022 who underwent coronary angiography and met ACS criteria were enrolled as study subjects. These included 36 cases of unstable angina (UA group), 36 cases of non-ST-segment elevation myocardial infarction (NSTEMI group), and 45 cases of ST-segment elevation myocardial infarction (STEMI group) (all considered ACS patients), with 39 non-ACS patients selected as the control group. Patient blood samples and general clinical data were collected, and plasma levels of NCL, C-reactive protein (CRP), and low-density lipoprotein cholesterol (LDL-C) were measured. Based on coronary angiography results, ACS patients were categorized into no lesion group, single-vessel disease group, double-vessel disease group, and multi-vessel disease group. According to ultrasonic echo characteristics, ACS patients were divided into vulnerable plaque group and stable plaque group, with patients without atherosclerotic plaques assigned to the no plaque group. The correlation between NCL expression levels and CRP and LDL-C in each ACS patient group was evaluated; the correlation between NCL and the number of diseased coronary vessels, severity of coronary artery disease, and Gensini score was analyzed; multivariate Logistic regression was employed to analyze whether plasma NCL

is an independent risk factor for ACS occurrence, and receiver operating characteristic (ROC) curve analysis was used to evaluate the optimal cutoff value of NCL for predicting ACS.

结果 NCL, LDL-C, and CRP levels in ACS patients in the UA, NSTEMI, and STEMI groups were significantly higher than those in the control group (P<0.05). NCL levels in the vulnerable plaque group (n=49) > stable plaque group (n=49) > no plaque group (n=33), and NCL levels were positively correlated with the degree of carotid plaque lesions (r=0.543, P<0.05). NCL levels in the coronary multi-vessel disease group (n=39) were higher than those in the double-vessel disease group (n=49) (P<0.05), and NCL levels in the coronary double-vessel disease group were higher than those in the single-vessel disease group (n=29) (P<0.05), with NCL levels positively correlated with the number of diseased coronary vessels (r=0.445, P<0.05). NCL levels in the high Gensini score group were significantly higher than those in the low and medium score groups (P<0.05), and the number of diseased coronary vessels was positively correlated with Gensini score (r=0.799, P<0.05). Multivariate Logistic regression analysis indicated that NCL is an independent risk factor for ACS, and ROC curve analysis showed that the optimal cutoff value for NCL was 0.765 ng/mL.

结论 Plasma NCL expression levels have certain clinical significance in evaluating plaque stability in ACS patients and provide reference value for ACS identification and risk stratification prediction. Plasma NCL levels are positively correlated with both the number of diseased coronary vessels and Gensini score, and plasma NCL level can serve as a reference indicator for predicting and assessing the severity of coronary artery disease to a certain extent. Elevated plasma NCL levels may be an independent risk factor for ACS occurrence and have predictive diagnostic value for ACS.

Full Text

Correlation of Plasma Nucleolin with Coronary Plaque Stability and Lesion Severity in Acute Coronary Syndrome

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Abstract

Background: Acute coronary syndrome (ACS) is a pathological clinical syndrome characterized by coronary atherosclerotic plaque rupture or erosion with

subsequent complete or incomplete thrombotic occlusion. The selection of specific and sensitive serological markers and detection methods holds important clinical value for rapid and accurate early diagnosis, condition assessment, and treatment implementation in ACS patients.

Objective: To investigate the relationship between plasma nucleolin (NCL) levels and coronary plaque stability/lesion severity in ACS patients, and to evaluate the predictive value of NCL for ACS.

Methods: A total of 117 patients hospitalized in the Cardiology Department of Changsha First Hospital in 2022 who underwent coronary angiography and met ACS diagnostic criteria were enrolled. Among them, 36 had unstable angina (UA group), 36 had non-ST-segment elevation myocardial infarction (NSTEMI group), and 45 had ST-segment elevation myocardial infarction (STEMI group). An additional 39 non-ACS patients served as controls. Blood samples and general clinical data were collected, and plasma levels of NCL, C-reactive protein (CRP), and low-density lipoprotein cholesterol (LDL-C) were measured. Based on coronary angiography results, ACS patients were categorized into no-lesion, single-vessel, double-vessel, and multi-vessel disease groups. According to ultrasonic echo characteristics, ACS patients were divided into vulnerable plaque and stable plaque groups, with those showing no atherosclerotic plaques classified as plaque-free. The correlations between NCL expression levels and CRP/LDL-C were evaluated across ACS groups. We analyzed the relationships between NCL and coronary lesion number, severity, and Gensini score. Multivariate logistic regression was used to determine whether plasma NCL constituted an independent risk factor for ACS, while ROC curve analysis assessed the optimal threshold for NCL in predicting ACS.

Results: NCL, LDL-C, and CRP levels were significantly higher in the UA, NSTEMI, and STEMI groups compared with controls ($P<0.05$). NCL levels positively correlated with LDL-C and CRP ($r=0.572$ and $r=0.639$, respectively; $P<0.05$). Comparison across carotid plaque severity groups revealed NCL levels in the vulnerable plaque group ($n=73$) > stable plaque group ($n=49$) > plaque-free group ($n=33$), with NCL levels positively correlating with carotid plaque severity ($r=0.543$, $P<0.05$). The multi-vessel disease group ($n=39$) showed higher NCL levels than the double-vessel group ($n=49$) ($P<0.05$), which in turn exceeded the single-vessel group ($n=29$) ($P<0.05$), demonstrating a positive correlation between NCL levels and coronary lesion number ($r=0.445$, $P<0.05$). The high Gensini score group exhibited significantly higher NCL levels than low and medium score groups ($P<0.05$), with coronary lesion number positively correlating with Gensini score ($r=0.799$, $P<0.05$). Multivariate logistic regression identified NCL as an independent risk factor for ACS. ROC curve analysis revealed an optimal cutoff value of 0.765 ng/mL for NCL.

Conclusion: Plasma NCL expression levels demonstrate clinical significance in evaluating plaque stability in ACS patients and offer reference value for ACS identification and risk stratification. Plasma NCL levels positively correlate with coronary lesion number and Gensini score, serving as a reference indicator

for predicting and assessing coronary lesion severity. Elevated plasma NCL may constitute an independent risk factor for ACS and holds predictive diagnostic value.

Keywords: Nucleolin; Acute coronary syndrome; Plaque stability; Coronary lesion severity

Introduction

Acute coronary syndrome (ACS) is a pathological clinical syndrome characterized by rupture or erosion of coronary atherosclerotic plaques with subsequent complete or incomplete thrombotic occlusion [1]. Rupture of vulnerable coronary plaques leading to thrombus formation represents the primary cause of mortality. Currently, most imaging techniques can only evaluate certain characteristics of susceptible plaques without reliably identifying vulnerable plaques or predicting their progression [2].

Many scholars now agree that bodily injury triggers atherosclerosis, initiating a cascade of inflammatory responses [3]. With rapid advances in detection technology and deeper exploration of inflammatory mechanisms, numerous novel serum biomarkers have been identified as associated with ACS formation and progression [4]. Carotid atherosclerotic plaque rupture commonly occurs in ACS patients beyond the systemic arterial system. Due to its superficial location and relatively low mobility, the carotid artery is frequently selected as a target vessel for vulnerable plaque research [5-6]. Therefore, examining the relationship between carotid plaque stability, lesion severity, and associated serum biomarker levels in ACS patients warrants investigation. Exploring the role of novel serological markers that should become detectable within hours of disease onset holds promise for predicting acute events and prognosis.

Nucleolin (NCL) is an evolutionarily conserved protein that shuttles between the nucleolus, cytoplasm, and cell membrane [7]. Intracellular nucleolin regulates nuclear functions while participating in the transport of various substances between the nucleus and cytoplasm. In recent years, nucleolin has also played an important regulatory role in apoptosis. While NCL expression has been extensively studied in tumor tissues [8], its plasma levels in cardiovascular diseases, particularly ACS, remain unreported. Building upon this research background and preliminary studies, this investigation employed enzyme-linked immunosorbent assay (ELISA) to detect plasma NCL content in ACS patients, analyzing its relationship with plaque stability, lesion severity, and ACS prediction to explore the significance of plasma NCL measurement in ACS pathogenesis and development.

Methods

Study Population We enrolled 117 patients hospitalized in the Cardiology Department of Changsha First Hospital in 2022 who completed coronary angiography and met ACS diagnostic criteria. The cohort included 36 patients with unstable angina (UA group), 36 with non-ST-segment elevation myocardial infarction (NSTEMI group), and 45 with ST-segment elevation myocardial infarction (STEMI group). An additional 39 non-ACS patients served as the control group.

Inclusion and Exclusion Criteria Inclusion criteria followed the "Guidelines for Rapid Emergency Diagnosis and Treatment of Acute Coronary Syndrome" [9]. This study was approved by the Ethics Committee of Changsha First Hospital (Approval No.: [2021] Ethics Review [Clinical] No. 32), and all participants provided informed consent. Exclusion criteria eliminated patients with acute/chronic inflammatory diseases, tumors, immunodeficiency, as well as pregnant or lactating women.

Instruments and Reagents Equipment included the Haimen Qilinbell TS-8 horizontal decolorization shaker, Thermo FRESCO 17 high-speed refrigerated centrifuge, and BioTek ELX800 microplate reader. Human nucleolin (NCL) ELISA kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd.

Data Collection and Laboratory Measurements General clinical data including gender, age, clinical symptoms, history of hypertension, diabetes, smoking, alcohol consumption, and family history were collected. Myocardial enzyme profiles, NCL, LDL-C, CRP, Gensini score, alanine aminotransferase (ALT), creatinine (Cr), blood glucose, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were analyzed based on medical records and original test reports.

Blood specimen collection and processing: On the morning following admission at 6 AM, 3 mL of blood was drawn from the median cubital vein (for thrombolysis or interventional patients, 3 mL was drawn before treatment). After collection, samples were left at room temperature for 1 hour, then centrifuged at 3,000 r/min for 15 minutes. Plasma was separated and stored at -70°C. Using the Roche Modular automatic biochemical analyzer, we measured blood glucose, TC, TG, ALT, Cr, HDL-C, LDL-C, myocardial enzyme profiles, and CRP from median cubital vein blood.

Plasma NCL detection: The following morning, 5 mL of fasting venous blood was drawn from ACS patients. Plasma was separated and stored at -20°C until analysis. Plasma NCL expression levels were measured by ELISA following kit instructions precisely. Test specimens were diluted 1:1 with sample diluent. Fifty microliters of diluted standards and 50 L of test samples were added to 96-well plates coated with NCL monoclonal antibody and incubated at 37°C for 2

hours before aspirating. Fifty microliters of biotin-labeled secondary antibody was added to each well and reacted at 37°C for 1 hour. Wells were washed three times with 0.01 M TBS washing solution (1 min each). Fifty microliters of substrate solution was added to each well, reacted at 37°C for 30 min with gentle mixing, then incubated at 37°C for 10 min protected from light. Stop solution was added to terminate the reaction, and optical density was measured immediately at 450 nm using a microplate reader.

Coronary Angiography and Gensini Score Coronary angiography was performed and interpreted by cardiologists in a standard catheterization laboratory. Based on patient characteristics, either radial or femoral artery access was selected. At least two views were obtained for the right coronary artery and at least four for the left coronary artery. Coronary stenosis severity and lesion branch number were determined and documented in procedure records. Gensini scores and coronary lesion numbers were calculated for each subject. The sum of lesion site scores yielded each patient' s total Gensini score. Using tertile classification, patients were categorized by Gensini score into mild (0-7 points, n=31), moderate (8-50 points, n=52), and severe (52-152 points, n=34) coronary stenosis groups. Based on coronary angiography results, ACS patients were divided into no-lesion, single-vessel, double-vessel, and multi-vessel disease groups.

Carotid Ultrasound Assessment Carotid ultrasound examination was performed using a Philips iE33 color Doppler ultrasound system with a 7-12 MHz ultra-wideband probe. Carotid plaque diagnostic criteria used the average intima-media thickness (IMT) from both sides, with IMT $\geq$ 1.2 mm or a thickness increase $\geq$ 0.5 mm compared with adjacent areas without luminal narrowing defined as plaque. Plaque stability was determined by two-dimensional ultrasound characteristics: fibrous plaques protruding into the lumen with clear boundaries and uniform echogenicity were considered stable and resistant to rupture, whereas plaques containing multiple components such as lipids, calcification, hemorrhage, and thrombus with heterogeneous internal echoes were deemed vulnerable and prone to rupture. ACS patients were categorized into vulnerable plaque, stable plaque, and plaque-free groups based on these ultrasound features.

Statistical Analysis Statistical analysis was performed using R software. Continuous variables with normal distribution were expressed as mean $\pm$ standard deviation ($\bar{x}\pm s$) and compared among multiple groups using one-way ANOVA. Categorical variables were expressed as percentages and analyzed using Pearson' s chi-square test. Pearson correlation analysis examined relationships between variables. Multivariate logistic regression identified independent risk factors. ROC curve analysis evaluated the clinical diagnostic value of plasma NCL. Statistical significance was defined as $P<0.05$.

Results

Baseline Characteristics Comparisons among control, UA, NSTEMI, and STEMI groups revealed significant differences in myocardial enzyme profiles, NCL, LDL-C, CRP, Gensini score, ALT, Cr, blood glucose, TC, TG, and HDL-C ($P<0.05$). No significant differences were observed in age, ALT, blood glucose, TC, TG, hypertension history, smoking history, or family history among the four groups ($P>0.05$) .

Correlations among NCL, LDL-C, and CRP Pearson correlation analysis demonstrated that plasma NCL levels positively correlated with LDL-C ($r=0.572$, $P<0.05$) and CRP ($r=0.639$, $P<0.05$). LDL-C also positively correlated with CRP ($r=0.456$, $P<0.05$).

NCL Levels and Carotid Plaque Stability The study included 33 plaque-free, 49 stable plaque, and 73 vulnerable plaque patients. Plasma NCL levels differed significantly among these three groups ($P<0.05$) . Pairwise comparisons showed that vulnerable plaque patients exhibited higher plasma NCL levels than both stable plaque and plaque-free groups, with stable plaque levels exceeding plaque-free levels ($P<0.05$). Pearson correlation analysis confirmed that plasma NCL levels positively correlated with carotid plaque severity ($r=0.543$, $P<0.05$).

NCL Levels and Coronary Lesion Characteristics The study comprised 39 no-lesion, 36 single-vessel, 36 double-vessel, and 45 multi-vessel disease patients. Significant differences in plasma NCL levels existed among these four groups ($F=28.763$, $P<0.001$). Pairwise comparisons revealed that multi-vessel disease patients had higher plasma NCL levels than double-vessel patients, who in turn exceeded single-vessel patients ($P<0.05$) .

Among mild ($n=31$), moderate ($n=52$), and severe ($n=34$) coronary stenosis groups, plasma NCL levels differed significantly ($F=23.701$, $P<0.001$). Pairwise comparisons showed that severe stenosis patients exhibited higher plasma NCL levels than moderate stenosis patients, who exceeded mild stenosis patients ($P<0.05$) . Pearson correlation analysis demonstrated that coronary lesion number positively correlated with Gensini score ($r=0.799$, $P<0.05$).

Multivariate Logistic Regression Analysis Using ACS outcome as the dependent variable (ACS patients=1, controls=0) and incorporating gender, age, hypertension history, diabetes history, smoking history, alcohol consumption history, family history, ALT, Cr, blood glucose, TC, TG, HDL-C, LDL-C, CRP, Gensini score, and myocardial enzyme profiles as independent variables, multivariate logistic regression analysis identified NCL, Gensini score, CRP, and ALT as risk factors for ACS: NCL (OR=3.195, 95%CI=1.131-9.026), Gensini score (OR=1.188, 95%CI=1.112-1.269), CRP (OR=1.799, 95%CI=1.325-2.443), and ALT (OR=1.081, 95%CI=1.010-1.156) .

ROC Curve Analysis The ROC curve for plasma NCL in predicting ACS yielded an area under the curve (AUC) of 0.818 (95%CI=0.729-0.907, P<0.05). The optimal cutoff value was 0.765 ng/mL, with specificity of 0.744, sensitivity of 0.906, and Youden index of 0.509 [Figure 1: see original paper].

Discussion

Nucleolin is a multifunctional phosphorylated protein in eukaryotic cells discovered in 1973 by Orrick et al. [10-12]. NCL exhibits widespread subcellular localization; changes in its distribution to different cellular compartments result in distinct functions. When cells are stimulated, NCL may participate in biological processes including apoptosis, proliferation, differentiation, inflammatory immunity, and vascular remodeling [13-14]. Research demonstrates that NCL shows higher expression in rapidly proliferating tissues and cells, with cell division rate positively correlating with NCL expression levels. High NCL expression in tumors and other rapidly dividing cells, contrasted with low levels in non-dividing cells, makes it an effective marker of cellular proliferation [15]. Studies have shown that angiotensin II induces significant upregulation of nucleolin expression and translocation from nucleus to cytoplasm and cell membrane, while NCL positively regulates vascular smooth muscle cell phenotype transformation, promoting VSMC transformation or proliferation and participating in vascular remodeling [15]. This suggests plasma NCL involvement in atherosclerosis development, with promotion of vascular remodeling potentially representing a risk factor for ACS.

Multiple studies indicate NCL participates in inflammatory responses with pro-inflammatory effects, suggesting it may constitute an important pro-inflammatory factor [20-21]. Our results show concurrent elevation of plasma NCL, LDL-C, and CRP levels in ACS patients, with pairwise positive correlations among all three markers (P<0.05). CRP and LDL-C levels were highest in the STEMI group, followed by NSTEMI, UA, and control groups. Since elevated CRP and LDL-C represent inflammatory status, this indirectly indicates more severe inflammatory responses in ACS patients compared with controls, suggesting NCL may directly promote inflammatory reactions in vulnerable plaques or indirectly regulate inflammatory factors to participate in ACS pathogenesis.

Research demonstrates that NCL on inflammatory cell membranes (such as THP-1 cells) participates in LPS-mediated inflammatory responses, while NCL antibodies inhibit LPS-induced secretion of TNF-α, IL-1β, and HMGB1, as well as phosphorylation of MAPK inflammatory signaling pathway components P38, JNK, and ERK [22]. Additional studies confirm that NCL on alveolar macrophage membranes may represent a novel membrane-bound receptor for LPS, participating in LPS internalization and inducing production and release of inflammatory factors TNF-α and IL-6, indicating membrane nucleolin involvement in LPS-induced signal transduction [23]. Other research shows NCL promotes IL-1β and TNF-α expression in cardiomyocytes, suggesting a pro-

inflammatory role in myocardial injury [24]. Whether nucleolin participates in regulating ACS inflammatory responses through MAPK pathways or modulates inflammatory factors such as IL-1β, IL-6, and TNF-α to influence ACS progression requires further investigation.

Comparison of plasma NCL levels across carotid plaque types revealed vulnerable plaque > stable plaque > plaque-free groups. Combined with correlation findings between NCL and inflammatory markers CRP and LDL-C, these results suggest plasma NCL holds clinical significance for evaluating plaque stability in ACS patients. We further analyzed correlations between plasma NCL levels and coronary lesion number/severity, finding positive correlations between NCL and both coronary lesion number and Gensini score. Multi-vessel disease patients exhibited higher plasma NCL than double-vessel and single-vessel patients, while severe stenosis patients showed higher levels than moderate and mild stenosis patients. These findings indicate elevated plasma NCL correlates positively with coronary lesion number and stenosis severity, suggesting plasma NCL elevation may serve as a predictor of coronary lesion severity.

Multivariate logistic regression analysis identified plasma NCL as an independent risk factor for ACS. ROC curve analysis preliminarily confirmed that plasma NCL levels >0.765 ng/mL yielded optimal predictive efficacy for ACS. Comprehensive analysis indicates elevated plasma NCL constitutes a risk factor for ACS, positively correlating with coronary lesion severity and serving as an important indicator for assessing coronary severity. NCL levels thus demonstrate clinical significance for evaluating plaque stability in ACS patients and may serve as a reference indicator for predicting coronary lesion severity and cardiovascular event risk.

This study had several limitations. The sample size of 117 ACS patients may be insufficient to fully reflect the clinical value of nucleolin in ACS, requiring larger ACS clinical samples for validation. Future research will expand the sample size and correlate NCL levels with GRACE (Global Registry of Acute Coronary Events) scores to investigate relationships between NCL levels and in-hospital mortality and risk stratification, aiming to provide evidence for early clinical diagnosis, treatment, and prognosis assessment in ACS patients.

Conclusion

Our findings preliminarily suggest that NCL levels may serve as an independent risk factor for ACS. Plasma NCL levels positively correlate with coronary lesion severity and may function as an important indicator for assessing coronary severity. NCL levels hold clinical significance for evaluating plaque stability in ACS patients and may provide a reference indicator for predicting coronary lesion severity and cardiovascular event risk.

Author Contributions

FANG Li proposed the main research objectives and took overall responsibility for the manuscript. ZHANG Qiongdan was responsible for study conception and design, implementation, and manuscript writing. MAO Zhuoni handled data collection, statistical analysis, and figure/table preparation. HUANG Dan contributed to manuscript revision.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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