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Value of serum NT-IGFBP-4 for non-invasive risk stratification of coronary heart disease and predictive efficiency for complexity of coronary artery lesions

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ABSTRACT

Background: We aimed to explore the value of serum N-terminal insulin-like growth factor-binding protein 4 (NT-IGFBP-4) in the non-invasive risk stratification of coronary heart disease and its predictive efficiency for the complexity of coronary artery lesions [assessed by Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) and SYNTAX II scores].

Methods: Subjects (180 in total) were recruited from patients treated between September 2023 and September 2024. Serum NT-IGFBP-4 level was measured. SYNTAX and SYNTAX II scores were assessed.

Results: The serum NT-IGFBP-4 level, SYNTAX score, and SYNTAX II score of the high-risk group were significantly higher than those of medium- and low-risk groups (p<0.001). The patients with more affected vessels had higher NT-IGFBP-4 levels. Univariate analysis of variance showed that NT-IGFBP-4 level was significantly different among the three risk groups (F=18.991, p<0.001), with a linear trend (p<0.001). Spearman rank correlation analysis showed that NT-IGFBP-4 level was positively correlated with the risk stratification (r=0.420, p<0.001). Multivariate logistic regression analysis showed that NT-IGFBP-4 level, SYNTAX score, and three-vessel disease were independent predictors of coronary artery lesions (p<0.05). ROC curve analysis showed that the areas under the curves of NT-IGFBP-4, SYNTAX score, and three-vessel disease were all >0.700.

Conclusions: Serum NT-IGFBP-4 reflects the pathophysiological state of coronary heart disease when combined with the SYNTAX II scoring system. It shows a significant positive correlation with the risk of coronary heart disease and can independently predict this risk.

Keywords: coronary heart disease, correlation, NT-IGFBP-4, risk stratification, scoring

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INTRODUCERE

Coronary heart disease severely jeopardizes human health [1], with increasing incidence and mortality rates yearly along with population ageing [2]. Coronary heart disease is attributed to coronary atherosclerosis, which refers to the gradual formation of atherosclerotic plaque owing to gradual deposition of lipids and other substances inside the blood vessel wall due to multiple factors-induced damage to the intima of coronary arteries, resulting in narrowing or blockage of blood vessels [3]. According to the data from the World Health Organization, coronary heart disease is one of the leading causes of death worldwide, with millions of people dying each year from this disease and its complications [4]. In China, coronary heart disease is a discouraging condition, and its onset risk is on the rise since unhealthy lifestyles like high-calorie, high-fat and high-salt diets and lack of exercise are increasingly common with the rapid development of the economy and the improvement of people's living standards, together with the intensification of the population aging [5,6].

Risk stratification of coronary artery disease is defined as the determination of the risk in patients through the assessment and classification of patients' condition based on such factors as clinical symptoms, risk factors, and severity of coronary artery disease [7]. However, risk stratification requires accurate markers and scoring systems. Recently, serum N-terminal insulin-like growth factor-binding protein 4 (NT-IGFBP-4), a product resulting from cleavage of IGFBP-4, has been closely implicated in the onset and progression of coronary heart disease [8]. Moreover, serum NT-IGFBP-4 also has a relationship to

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the apoptosis and repair of cardiomyocytes, affecting the cardiac function of patients with coronary heart disease [9]. Hence, serum NT-IGFBP-4 is expected to become a novel biomarker for coronary heart disease, rendering new ideas and methods for diagnosis and treatment.

The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) II scoring system, an anatomical scoring system for coronary artery lesions, is improved and perfected based on the SYNTAX scoring system, which comprehensively considers the anatomical characteristics of coronary artery lesions as well as the clinical characteristics and comorbidities of patients [10,11]. The SYNTAX II scoring system requires a detailed analysis and assessment of coronary angiography results mainly involving anatomical features (e.g. lesion location, lesion length, stenosis degree, calcification extent, bifurcation lesions, and chronic total occlusion), as well as clinical characteristics (e.g. age, gender, cardiac function, renal function, and diabetes mellitus) and comorbidities (hypertension for example) of patients. By comprehensively assessing the aforementioned factors, a SYNTAX II score can be acquired, and a higher score denotes a higher degree of lesion complexity and prognostic risk of patients.

Given this, we herein explored the value of serum NT-IGFBP-4 in the non-invasive risk stratification of coronary heart disease and its predictive efficiency for the complexity of coronary artery lesions assessed by SYNTAX and SYNTAX II scores.

METHODS

Study subjects

Subjects were selected from patients with coronary heart disease treated herein from September 2023 to September 2024. All patients were diagnosed based on coronary angiography. Exclusion criteria: patients with severe hepatic or renal insufficiency, malignant tumors, or infectious diseases; those without coronary artery lesions. Their baseline clinical data were recorded.

Risk stratification of coronary heart disease

Subjects were assigned to a low-risk group, a medium-risk group or a high-risk group based on their clinical symptoms, electrocardiograms, cardiac enzymes, cardiac ultrasound results and other examination results. The specific criteria for stratification are as follows:

Low-risk group: Patients did not present evident clinical symptoms or only had mild chest pain, chest tightness and other symptoms, without prominent abnormalities in electrocardiograms, cardiac enzymes, cardiac ultrasound results and other examination results.

Medium-risk group: Patients suffered from such moderate symptoms as moderate chest pain and moderate chest tightness, accompanied by mild abnormalities in electrocardiograms, cardiac enzymes, cardiac ultrasound results and other examination results.

High-risk group: Patients had severe chest pain, chest tightness and so on, with obvious abnormalities in electrocardiograms, cardiac enzymes, cardiac ultrasound results and other examination results.

Serum NT-IGFBP-4 measurement

Fasting venous blood (5 mL) was harvested from patients before coronary angiography into a test tube without anticoagulant, followed by centrifugation at a speed of 3000 rpm for 10 min at room temperature. Afterwards, the serum was separated and stored in a refrigerator at -80°C for later testing. Enzyme-linked immunosorbent assay was carried out strictly in accordance with the kit instructions, with standards and blank controls set up. A microplate reader was employed to read the absorbance value, and the concentration of serum NT-IGFBP-4 (ng/mL) was calculated based on the standard curve.

Assessment of coronary artery lesions

Two independent cardiovascular interventional physicians used standard multi-position coronary angiography (including at least left anterior oblique, right anterior oblique, head, and foot positions) to evaluate coronary artery lesions.

Number of affected vessels: The number of affected coronary arteries (one-, two-, three-vessel diseases; left main trunk disease was considered as two-vessel disease) was recorded.

SYNTAX score: SYNTAX score was calculated based on the anatomical characteristics of coronary artery lesions (lesion location, length, degree of stenosis, calcification, bifurcation lesions, chronic total occlusion, etc.).

SYNTAX II score: Based on the SYNTAX score, clinical characteristics (age, gender, LVEF, renal function, diabetes, hypertension, etc.) were included for a comprehensive score ranging from 0 to 83 points. A higher score meant the lesion was more complex and the prognostic risk was higher.

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software. Measurement data were expressed as mean ± standard deviation. One-way analysis of variance was used for comparison between groups. If the variance was heterogeneous, the Welch test was used. The Tukey method was used for pairwise comparison. Count data were expressed as percentages. The chi-square test or Fisher's exact probability method was utilized for com-

parison between groups. Spearman's rank correlation was employed to analyze the correlation between the NT-IGFBP-4 level and the SYNTAX II score. Multivariate logistic regression was performed to analyze the independent predictive value of NT-IGFBP-4 level for high-risk SYNTAX II score (≥33 points, defined as high-risk threshold), and the odds ratio (OR) and 95% confidence interval (CI) were calculated. Receiver operating characteristic (ROC) curves were plotted to compare the diagnostic efficiencies of factors such as NT-IGFBP-4 and SYNTAX score for high-risk SYNTAX II score, and the Delong test was used to compare the area under the curve (AUC). $p<0.05$ was considered statistically significant.

RESULTS

General data

According to comparisons of general data among the three groups (n=180 in total), the age, gender, smoking history, drinking history, hypertension, diabetes mellitus, LVEF and creatinine were of no significant differences among the three risk groups ($p>0.05$) (Table 1).

NT-IGFBP-4 and the risk of coronary heart disease

The serum NT-IGFBP-4 level, SYNTAX score, and SYNTAX II score of the high-risk group were significantly higher than those of medium- and low-risk groups ($p<0.001$). The patients with more affected vessels had higher NT-IGFBP-4 levels. Univariate analysis of variance showed that NT-IGFBP-4 level was significantly different among the three risk groups (F=18.991, $p<0.001$), with a linear trend ($p<0.001$). Spearman rank correlation analysis showed that NT-IGFBP-4 level was positively correlated with the risk stratification (r=0.420, $p<0.001$) (Table 2 and Figure 1).

Predictive value of serum NT-IGFBP-4

Multivariate logistic regression analysis was performed with high-risk SYNTAX II score as the dependent variable (high risk = 0, low-intermediate risk = 1), while including NT-IGFBP-4 level, SYNTAX score, and three-vessel disease. The results showed that NT-IGFBP-4 level, SYNTAX score, and three-vessel disease were independent predictors of coronary artery disease (Table 3).

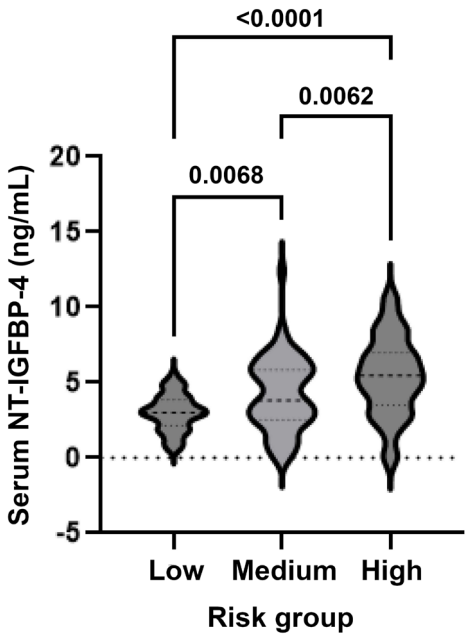

Figure 1. NT-IGFBP-4 levels across groups of CHD non-invasive risk stratification

Table 1. General data of the three risk groups

Item		Low-risk (n=60)	Medium-risk (n=60)	High-risk (n=60)	Statistical value	*p* value
Sex	Male	43 (71.67)	42 (70.00)	46 (76.67)	χ^2=0.729	0.695
	Female	17 (28.33)	18 (30.00)	14 (23.33)		
Age (years)		58.28 ± 7.40	56.44 ± 7.59	59.14 ± 8.21	F=1.905	0.152
Smoking history	Yes	39 (65%)	41 (68%)	43 (71%)	χ^2=0.616	0.735
	No	21 (35%)	19 (31%)	17 (28%)		
Drinking history	Yes	45 (75%)	44 (73%)	47 (78%)	χ^2=0.421	0.810
	No	15 (25%)	16 (26%)	13 (21%)		
Hypertension	Yes	46 (76%)	45 (75%)	50 (83%)	χ^2=1.374	0.502
	No	14 (23%)	15 (25%)	10 (16%)		
Diabetes mellitus	Yes	23 (38%)	25 (41%)	29 (48%)	χ^2=1.271	0.530
	No	37 (61%)	35 (58%)	31 (51%)		
LVEF (%)		53.11 ± 7.82	51.53 ± 8.22	52.03 ± 8.63	F=0.577	0.562
Creatinine (μmol/L)		85.26 ± 11.36	87.13 ± 12.36	86.95 ± 12.23	F=0.444	0.642

Table 2. Serum NT-IGFBP-4 level, SYNTAX score, SYNTAX II score and affected vessels

Item	Low-risk group (n=60)	Medium-risk group (n=60)	High-risk group (n=60)	F	*p* value
Serum NT-IGFBP-4 (ng/mL)	3.01 ± 1.21	4.21 ± 2.41	5.43 ± 2.57	18.991	0.001
SYNTAX score	15.33 ± 3.12	18.60 ± 4.13	22.11 ± 5.74	36.641	0.001
SYNTAX II score	18.21 ± 3.41	26.54 ± 4.21	38.45 ± 5.41	17.754	0.001
Three-vessel disease	3 (5%)	15 (25%)	33 (55%)	25.404	0.001

Table 3. Predictive value of serum NT-IGFBP-4 level for complexity of coronary artery lesions

Indicator	B	Standard error	Wald	Significance	EXP (B)	95% confidence interval
Serum NT-IGFBP-4	-0.380	0.086	19.452	0.001	0.684	0.577-0.809
SYNTAX score	-0.338	0.086	15.624	0.001	0.713	0.603-0.843
Three-vessel disease	-1.816	0.419	18.751	0.001	0.163	0.072-0.370
Constant	4.510	0.682	43.731	0.001	90.927	

Table 4. Diagnostic efficiencies of different indicators for high-risk SYNTAX II score

Factor	AUC	95% confidence interval	Cut-off value	*p* value	Sensitivity	Specificity	Youden index
Serum NT-IGFBP-4	0.716	0.631-0.800	4.690	0.001	0.733	0.717	0.450
SYNTAX score	0.718	0.634-0.801	3.065	0.001	0.717	0.700	0.417
Three-vessel disease	0.700	0.614-0.786	-	0.001	0.550	0.850	0.400

Diagnostic efficiencies of different indicators

ROC curve analysis showed that the AUC values of NT-IGFBP-4, SYNTAX score, and three-vessel disease for high-risk SYNTAX II score were all >0.700, indicating high diagnostic values (Table 4 and Figure 2).

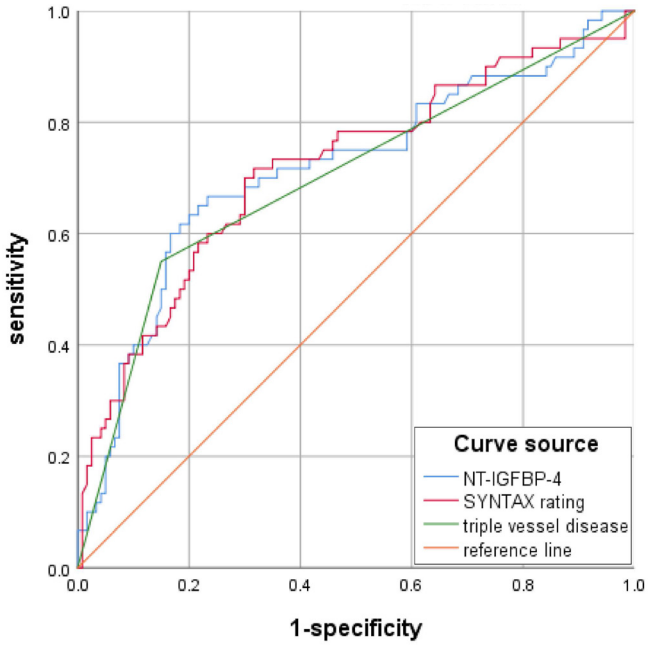

Figure 2. ROC curves for diagnostic efficiencies of different indicators for high-risk SYNTAX II score

DISCUSSION

Coronary heart disease serves as one of the major contributors to death and disability worldwide, especially in low- and middle-income countries and older populations [12,13]. Its accurate risk stratification is of great significance for formulating individualized therapeutic regimens, assessing patient prognosis, and rationally allocating medical resources in clinical practice. Traditional risk stratification of coronary artery disease is based on such factors as clinical symptoms, electrocardiogram findings, and markers of myocardial injury in most cases, which, however, fails to fully and accurately reflect the complexity of coronary artery disease and the severity of myocardial ischemia [14-16]. The SYNTAX II scoring system has been further improved and perfected based on the SYNTAX scoring system originally applied to evaluate the complexity of coronary artery lesions, which lays increased emphasis on the detailed characterization and comprehensive assessment of coronary artery lesions and is capable of reflecting the true situation of coronary artery lesions more accurately [17-19]. Serum NT-IGFBP-4, a biomarker that has attracted much attention in recent years, acts as a vital regulatory factor in the cardiovascular system [20].

In the present study, the serum NT-IGFBP-4 level, SYNTAX score, and SYNTAX II score of the high-risk group were significantly higher than those of medium- and low-risk groups. This suggests that with the gradual increase in the risk of coronary heart disease, the complexity of coronary artery disease is also increasing, and myocardial ischemia is becoming more severe. Accordingly, the secretion of serum NT-IGFBP-4 also increases, thus taking part in stress responses and cardiovascular repair process. Moreover, the NT-IGFBP-4 level was positively correlated with the risk stratification. The SYNTAX II scoring system mainly quantitatively assesses coronary artery lesions from the perspective of anatomical structure and lesion characteristics of blood vessels, which can reflect the severity and complexity of coronary artery lesions [21]. The positive correlations observed herein suggest that during the progression of coronary heart disease, the variations in vascular structure and the abnormal secretion of cytokines are interrelated and interactional, jointly boosting the evolution of coronary heart disease from a low-risk state to a high-risk state.

Furthermore, multivariate logistic regression analysis showed that NT-IGFBP-4 level, SYNTAX score, and three-vessel disease were independent predictors of coronary artery lesions. Therefore, the combined use of anatomical assessment (SYNTAX II score) and biological marker (NT-IGFBP-4) can improve the accuracy of risk stratification. From a pathophysiological perspective, there is a synergistic effect between the vascular structural changes reflected by the SYNTAX II score and the abnormal cytokine secretion mediated by NT-IGFBP-4: complex

vascular lesions can induce myocardial ischemia and inflammatory response, thereby promoting the release of NT-IGFBP-4; and the increase in NT-IGFBP-4 can aggravate vascular damage, forming a vicious cycle. By comprehensively evaluating these factors, the risk stratification and prognosis of patients with coronary heart disease can be more accurately determined [20]. In addition, the specificity of three-vessel disease for high-risk stratification in this study was as high as 85.0%, further highlighting the importance of lesion range to risk assessment, and NT-IGFBP-4 can work as a supplementary indicator for lesion changes.

Nevertheless, this study still has limitations. For example, the sample size was small. Additionally, this study only explored the correlation between NT-IGFBP-4 level and risk stratification of coronary heart disease, but did not explore the specific pathophysiological mechanism in depth. Future studies with larger sample sizes are needed to enhance the generalizability and reliability of our findings.

CONCLUSIONS

In conclusion, serum NT-IGFBP-4 reflects the pathophysiological state of coronary heart disease when combined with the SYNTAX II scoring system. It shows a significant positive correlation with the risk of coronary heart disease and can independently predict this risk.

ABBREVIATIONS

AUC – area under the curve

CI – confidence interval

LVEF – left ventricular ejection fraction

NT-IGFBP-4 – N-terminal insulin-like growth factor-binding protein 4

PCI – percutaneous coronary intervention

ROC – receiver operating characteristic

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AUTHORS' CONTRIBUTION

HL – study design, data analysis, writing

XG – data collection, data analysis

SY – data collection

FX – data analysis

HL – data analysis

HZ – study design, data collection

CONFLICT OF INTEREST

None to declare.

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