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Serum Levels of Cystatin C, N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), and Cardiac Function in Patients with Unstable Angina Pectoris

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This study aimed to investigate the association between serum levels of cystatin C, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and cardiac function in patients with unstable angina pectoris (UAP).

Material/Methods: A cross-sectional observational study was conducted at a single center and recruited 300 patients (214 men and 86 women), who were diagnosed with UAP between June 2018 to December 2018. The patients had serum levels of NT-ProBNP measured and were divided into four groups according to the serum levels of cystatin C: Q1, 0.49–0.83 mg/L; Q2, 0.84–1.04 mg/L; Q3, 1.05–1.38 mg/L; Q4, 1.39–4.21 mg/L. Cardiac function was graded according to the New York Heart Association (NYHA) class I to IV criteria.

Results: In the 300 patients with UAP, there were significant differences in cardiac function and NT-ProBNP levels between the four study groups (Q1 to Q4) ($p<0.05$). Univariate analysis showed that body weight, heart rate, treatment with aspirin, ticagrelor, angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker (ACE/ARB), diuretic use, uric acid level, and serum cystatin C levels were significantly associated with increased levels of NT-ProBNP. After adjusting for confounding factors screened in univariate analysis, multivariate regression analysis showed that increased serum cystatin C levels were significantly associated with increased levels of NT-ProBNP.

Conclusions: Increased serum levels of cystatin C were associated with poor cardiac function and increased levels of NT-ProBNP in patients with UAP.

MeSH Keywords: Angina, Unstable • Cystatin C • Natriuretic Peptide, Brain

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Background

Coronary heart disease (CHD) is a common clinical condition that is caused by coronary artery atherosclerosis [1–5], which leads to coronary artery spasm, stenosis, or occlusion. CHD includes myocardial ischemia [6], myocardial hypoxia [7], and myocardial infarction. The symptoms of acute CHD include chest tightness, chest pain, and other clinical symptoms. Recently, epidemiological studies have shown that the morbidity and mortality from CHD continue to rise, and the onset of CHD occurs at a younger age [8–10]. Unstable angina pectoris (UAP) is a type of CHD, which commonly presents acutely to the department of cardiology, and can be associated with sudden cardiac death [11,12]. The pathogenesis of UAP includes platelet activation, adhesion, and aggregation associated with advanced atherosclerosis of the coronary artery [13,14].

Clinical research studies have identified the risk factors associated with UAP, which include the frequency of attacks of UAP [15], the serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) [16,17], and the levels of inflammatory mediators [18,19], which may have diagnostic and prognostic roles. However, the morbidity and mortality of patients with UAP remains high and results in a social and healthcare economic burden. Therefore, there is a need for new serological markers to refine the stratification of the risk of UAP and improve long-term patient prognosis.

Cystatin C is a cysteine protease inhibitor secreted by nucleated cells [20–22]. Under normal physiological conditions, cystatin C can be completely filtered by the renal glomerulus and is not affected by age, gender, or liver function. Several previous studies have shown that cystatin C is affected factors that include thyroid function [23,24], diabetes mellitus [25], and cardiovascular disease [26], and is independent of kidney function. Cystatin C regulates the activity of cysteine protease *in vivo* and participates in the dynamic balance of the extracellular matrix (ECM) production and degradation. Cystatin C has a role in vascular wall remodeling at the level of protein metabolism and is correlated with the prevalence and incidence of cardiovascular disease [27–29]. Recent studies have shown that cystatin C is involved in the formation of atherosclerotic plaque rupture and restenosis, and is also significantly related to myocardial infarction and sudden cardiac death in patients with CHD [27–29].

However, roles for cystatin C, NT-ProBNP, and cardiac function in patients with UAP remain unknown. Therefore, this study aimed to investigate the association between serum levels of cystatin C, NT-proBNP, and cardiac function in patients with UAP at a single center in China.

Material and Methods

Patients

A cross-sectional study included patients with unstable angina pectoris (UAP) diagnosed in the First Affiliated Hospital of Guangxi Medical University from June 2018 to December 2018. The inclusion criteria were patient age ≥18 years and a diagnosis of UAP according to clinical symptoms, electrocardiogram findings, laboratory results, and coronary angiography. The exclusion criteria included a history of acute myocardial infarction, including ST-segment elevation myocardial infarction (STEMI) and non-STEMI, a history of malignancy or infection, autoimmune disease, endocrine disorders, and hematological disease. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Approval No: 2019. KY-E-103).

Patient data

Patient data were collected from the electronic medical record system of the First Affiliated Hospital of Guangxi Medical University, including the basic clinical and demographic characteristics, clinical symptoms, and examination results. Data collected for each patient included gender, age, height, weight, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), uric acid level, fasting blood glucose level, 2-hour postprandial blood glucose level, glycosylated hemoglobin, cystatin C, N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), smoking history, history of drinking alcohol, marital status, history of disease, and medication history. The basic clinical and demographic characteristics of the patients were collected during a face-to-face meeting between the patient and cardiovascular internal medicine nurses. The results of laboratory tests were obtained from venous blood drawn within 24 hours after admission. Laboratory tests, including for cystatin C and NT-proBNP, were undertaken by the Laboratory Department of the First Affiliated Hospital of Guangxi Medical University. Cardiac echocardiography was performed by a physician in the Department of Echocardiography. Cardiovascular physicians performed the electrocardiograms and coronary angiography.

Patient groups

Patients were divided into four groups according to the serum levels of cystatin C levels that were measured within 24 hours after hospital admission. The study groups included group Q1 with a cystatin C level of 0.49–0.83 mg/L, group Q2 with a cystatin C level of 0.84–1.04 mg/L, group Q3 with a cystatin C level of 1.05–1.38 mg/L, and group Q4 with a cystatin C level of 1.39–4.21 mg/L. Cardiac function was assessed using the New York Heart Association (NYHA) classification. Serum NT-ProBNP

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levels were measured and compared between the four groups. The differences were expressed as the odds ratio (OR) and 95% confidence interval (CI).

Statistical analysis

Continuous variables that conformed to a normal distribution were expressed as the mean±standard deviation (SD), and the differences between groups were compared using the least significant difference (LSD) variance analysis. The median and quartile represented continuous variables that did not conform to a normal distribution. The rank-sum test was used to compare groups. The number and percentage expressed categorical variables. The chi-squared (χ^2) test was used for comparison between the study groups. Pearson correlation analysis was used for the correlation between cystatin C and NT-ProBNP. Considering the skewed distribution of NT-ProBNP, the NT-ProBNP results were converted into $\log_{10}$ transformed NT-ProBNP. Univariate analysis was used for the variables associated with NT-ProBNP. Also, NT-ProBNP was a dependent variable, cystatin C was an independent variable, and the variables selected from univariate analysis as covariates were adjusted in multivariate regression analysis to identify the correlation between cystatin C and NT-ProBNP. Data were analyzed using SPSS version 22.0 statistical software (IBM, Chicago, IL, USA) and R statistical software. A P-value <0.05 was considered to be statistically significant.

Results

Baseline characteristics of patients with unstable angina pectoris (UAP) in the four study groups

There were 300 patients in the study, including 214 men and 86 women, who were divided into four groups, Q1 to Q4, according to the serum levels of cystatin C: Q1, 0.49–0.83 mg/L; Q2, 0.84–1.04 mg/L; Q3, 1.05–1.38 mg/L; Q4, 1.39–4.21 mg/L. The heart rate, uric acid level, fasting blood sugar, marital status, atrial fibrillation, cerebral infarction, history of percutaneous coronary intervention (PCI), angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor antagonist (ARB), calcium channel blockers (CCBs), and diuretics were not significantly different between the four groups (all P<0.05). However, there were significant differences in cardiac function and N-terminal pro-B-type natriuretic peptide (NT-proBNP) between the four groups (all P<0.05). Also, with the increase in cystatin C, the New York Heart Association (NYHA) cardiac function classification (I to IV), and the NT-ProBNP levels also showed an increasing trend (Figure 1). There was no difference in other indicators between the four groups (all, P>0.05) (Table 1).

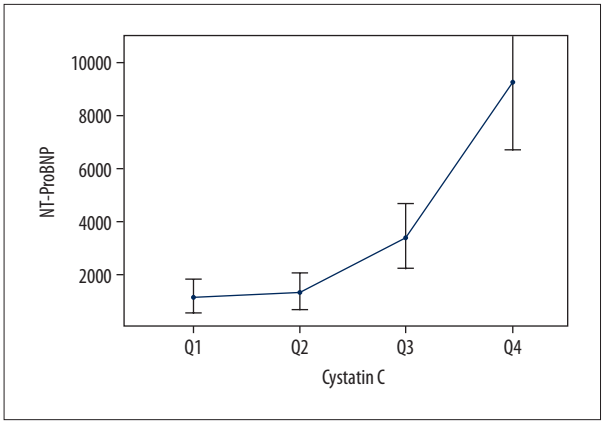

Figure 1. Comparison of the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the four study groups, Q1 to Q4, according to the serum levels of cystatin C.

Comparison of cystatin C levels in patients with different cardiac functions (NYHA)

There was a significant difference in cystatin C levels between the four study groups (P<0.05), and with the increasing cardiac function, cystatin C levels also showed an increasing trend (Figure 2).

Univariate analysis of factors associated with NT-ProBNP levels

Univariate analysis showed that weight, heart rate, aspirin treatment, ticagrelor treatment, the use of an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker (ACE/ARB), the use of diuretics, uric acid levels, and cystatin C levels (Q2 *vs.* Q1: OR, 157.28; 95% CI, –1932.17–2246.73; Q3 *vs.* Q1: OR, 2242.92; 95% CI, 173.10–4312.73; Q4 *vs.* Q1: OR, 8055.23; 95% CI, 5965.78–10144.68) were significantly associated with NT-ProBNP levels. However, other variables are not associated with NT-ProBNP (Table 2).

Multivariate analysis of cystatin C and NT-ProBNP

The NT-ProBNP was a dependent variable, and cystatin C was an independent variable. The variable with a significant difference in univariate analysis was the covariate in multivariate regression analysis. In the adjusted model, the weight, heart rate, aspirin, the use of ticagrelor, ACEI/ARB, and diuretics were adjusted, and the results showed that there was a correlation between cystatin C and NT-ProBNP (Q2 *vs.* Q1: OR, 78.74; 95% CI, –1882.76–2040.25; Q3 *vs.* Q1: OR, 604.38; 95% CI, –1378.63–2587.40; Q4 *vs.* Q1: OR, 6727.24; 95% CI, 4599.70–8854.77). In the adjusted II model, weight, heart rate, the use of aspirin, ticagrelor, ACEI/ARB, diuretics, and uric acid were adjusted, and this association remained (Q2 *vs.* Q1:

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Table 1. Baseline characteristics of patients in the four study groups (Q1 to Q4) and the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Study groups (Q1 to Q4) according to serum cystatin C levels	Q1	Q2	Q3	Q4	P-value
N	71	76	78	75	
Age (years)	64.70±13.55	63.95±14.27	64.10±13.17	65.96±12.94	0.791
Height (cm)	163.60±7.95	162.62±8.49	161.41±13.98	161.51±7.87	0.516
Weigh (kg)	64.37±11.15	63.62±11.98	63.93±9.97	62.77±11.01	0.862
Heart rate (bpm)	80.30±14.34	76.46±15.14	84.67±18.12	81.52±20.93	0.034
SBP (mmHg)	134.00±22.56	132.54±21.66	128.47±20.08	131.23±24.50	0.473
DBP (mmHg)	87.41±76.22	75.99±13.04	76.60±12.56	73.87±13.41	0.152
Uric acid (μmol/L)	333.25±113.24	387.78±104.25	422.92±116.08	521.93±141.93	<0.001
Fasting blood sugar (mmol/L)	6.85±3.17	5.63±1.89	5.84±1.98	6.30±2.58	0.021
2-hour postprandial blood glucose (mmol/L)	9.39±4.22	8.62±3.59	9.39±4.03	9.00±2.72	0.643
Glycosylated hemoglobin (%)	7.11±1.82	6.58±1.39	6.76±1.69	6.84±1.26	0.311
NT-ProBNP (pg/ml)	265.00 (71.00–1057.50)	333.00 (96.19–1307.50)	1113.00 (257.95–4555.50)	5222.00 (1014.00–13898.00)	<0.001
Left ventricular ejection fraction (%)	60.86±12.26	60.16±12.67	63.90±11.98	60.68±14.78	0.269
Sex (male, n, %)	48 (67.61%)	56 (73.68%)	58 (74.36%)	52 (69.33%)	0.757
Smoking (n, %)					0.997
No	15 (21.13%)	19 (25.00%)	19 (24.36%)	17 (22.67%)	
Yes	37 (52.11%)	37 (48.68%)	37 (47.44%)	38 (50.67%)	
Never	19 (26.76%)	20 (26.32%)	22 (28.21%)	20 (26.67%)	
Drinking (n, %)					0.445
No	18 (25.35%)	19 (25.00%)	18 (23.08%)	19 (25.33%)	
Yes	44 (61.97%)	47 (61.84%)	54 (69.23%)	41 (54.67%)	
Never	9 (12.68%)	10 (13.16%)	6 (7.69%)	15 (20.00%)	
Marital status (n,%)					0.010
Yes	67 (94.37%)	75 (98.68%)	75 (96.15%)	68 (90.67%)	
No	2 (2.82%)	0 (0.00%)	1 (1.28%)	0 (0.00%)	
Widowed	2 (2.82%)	0 (0.00%)	1 (1.28%)	0 (0.00%)	
Divorce	0 (0.00%)	1 (1.32%)	1 (1.28%)	7 (9.33%)	
Hypertension (yes, n, %)	38 (53.52%)	46 (60.53%)	42 (53.85%)	54 (72.00%)	0.072
Diabetes (yes, n, %)	24 (33.80%)	23 (30.26%)	24 (30.77%)	30 (40.00%)	0.565
Atrial fibrillation (yes, n, %)	1 (1.41%)	3 (3.95%)	7 (8.97%)	14 (18.67%)	<0.001
Cerebral infarction (yes, n, %)	3 (4.23%)	12 (15.79%)	4 (5.13%)	10 (13.33%)	0.034
Cerebral hemorrhage (yes, n, %)	0 (0.00%)	1 (1.32%)	0 (0.00%)	0 (0.00%)	0.398

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Table 1 continued. Baseline characteristics of patients in the four study groups (Q1 to Q4) and the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Study groups (Q1 to Q4) according to serum cystatin C levels	Q1	Q2	Q3	Q4	P-value
History of PCI (yes, n, %)	9 (12.68%)	23 (30.26%)	20 (25.64%)	25 (33.33%)	0.024
History of CABG (yes, n, %)	0 (0.00%)	1 (1.32%)	0 (0.00%)	1 (1.33%)	0.575
NYHA (n, %)					<0.001
Class I	52 (73.24%)	46 (60.53%)	39 (50.00%)	28 (37.33%)	
Class II	12 (16.90%)	18 (23.68%)	15 (19.23%)	11 (14.67%)	
Class III	5 (7.04%)	9 (11.84%)	15 (19.23%)	20 (26.67%)	
Class IV	2 (2.82%)	3 (3.95%)	9 (11.54%)	16 (21.33%)	
Aspirin (yes, n, %)	62 (88.57%)	63 (82.89%)	71 (91.03%)	56 (74.67%)	0.029
Clopidogrel (yes, n, %)	38 (55.07%)	47 (61.84%)	51 (65.38%)	43 (58.11%)	0.603
Ticagrelor (yes, n, %)	28 (40.00%)	26 (34.21%)	22 (29.33%)	15 (20.00%)	0.061
ACEI/ARB (yes, n, %)	51 (72.86%)	59 (77.63%)	59 (76.62%)	37 (49.33%)	<0.001
β-blocker (yes, n, %)	55 (78.57%)	60 (80.00%)	59 (75.64%)	54 (72.00%)	0.670
CCB (yes, n, %)	15 (21.43%)	25 (32.89%)	17 (22.37%)	33 (44.00%)	0.008
Diuretic (yes, n, %)	21 (30.00%)	35 (46.05%)	47 (60.26%)	60 (80.00%)	<0.001

Continuous variables conforming to a normal distribution expressed as the mean±standard deviation (SD). Continuous variables not conforming to a normal distribution expressed as the median (quartile). Numerical data expressed as the number and percentage (%). Study groups according to cystatin C levels: Q1, 0.49–0.83 mg/L; Q2, 0.84–1.04 mg/L; Q3, 1.05–1.38 mg/L; Q4, 1.39–4.21 mg/L. SBP – systolic blood pressure; DBP – diastolic blood pressure; PCI – percutaneous coronary intervention; CABG – coronary artery bypass surgery; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor antagonist; CCB – calcium channel blocker; NYHA – New York Heart Association.

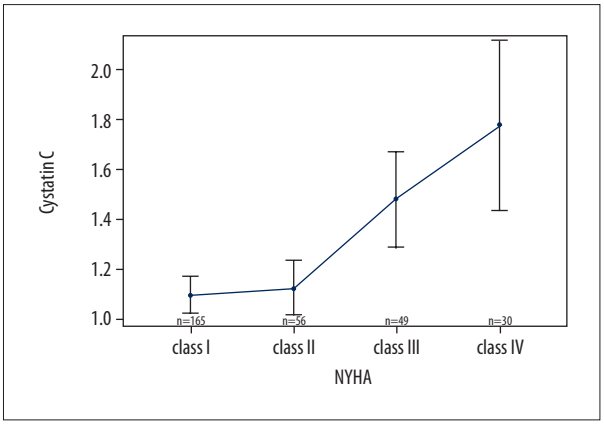

Figure 2. Comparison of the serum levels of cystatin C in patients with New York Heart Association (NYHA) class I to IV cardiac function.

OR, –260.98; 95% CI, –2268.21–1746.25; Q3 *vs.* Q1: OR, 531.23; 95% CI, –1559.07–2621.53; Q4 *vs.* Q1: OR, 5163.41; 95% CI, 2563.76–7763.05) (Table 3).

Pearson correlation analysis of cystatin C and NT-ProBNP

Statistical analysis showed that the results for NT-ProBNP levels showed a skewed distribution, and so NT-ProBNP data were converted to $\log_{10}$. Pearson correlation analysis showed a significant relationship between cystatin C and BT-ProBNP (r=0.4875; P<0.001) (Figure 3).

Discussion

This study was conducted at a single center in China and aimed to investigate the association between serum levels of cystatin C, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and cardiac function in patients with unstable angina pectoris (UAP). The study findings identified a significant association

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Table 2. Univariate analysis of the associations with serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

	NT-ProBNP	
	OR (95% CI)	P-value
Gender		
Male	Reference	
Female	1279.53 (–489.72–3048.79)	0.1574
Age (years)	2.83 (–5.97–11.63)	0.5293
Height (cm)	–22.81 (–106.98–61.36)	0.5957
Weight (kg)	–103.19 (–180.06– –26.31)	0.0090
Heart rate (bpm)	104.90 (61.09–148.72)	<0.0001
SBP (mmHg)	–13.33 (–49.87–23.21)	0.4752
DBP (mmHg)	–2.68 (–23.51–18.16)	0.8014
Smoking (n, %)		
No	Reference	
Yes	–29.64 (–2048.75–1989.47)	0.9771
Never	–427.69 (–2717.89–1862.50)	0.7146
Alcohol (n, %)		
No	Reference	
Yes	16.14 (–1904.28–1936.56)	0.9869
Never	10.99 (–2718.01–2739.99)	0.9937
Marital status (n, %)		
Yes	Reference	
No	–2141.48 (–10283.99–6001.03)	0.6066
Widowed	5137.82 (–3004.69–13280.33)	0.2172
Divorce	–582.74 (–5096.09–3930.60)	0.8004
Hypertension (n, %)		
No	Reference	
Yes	1214.94 (–429.45–2859.33)	0.1486
Diabetes (n, %)		
No	Reference	
Yes	582.96 (–1121.06–2286.97)	0.5030
Atrial fibrillation (n, %)		
No	Reference	
Yes	2422.07 (–442.08–5286.23)	0.0985
Cerebral infarction (n, %)		
No	Reference	
Yes	971.25 (–1724.59–3667.09)	0.4806
Cerebral hemorrhage (n, %)		
No	Reference	
Yes	–2640.96 (–16688.30–11406.37)	0.7128
History of PCI (n, %)		
No	Reference	
Yes	–1228.96 (–3066.86–608.94)	0.1910
History of CABG (n, %)		
No	Reference	
Yes	–2922.04 (–12868.26–7024.19)	0.5652
Aspirin (n, %)		
No	Reference	
Yes	–4938.62 (–7117.27– –2759.97)	<0.0001
Clopidogrel (n, %)		
No	Reference	
Yes	–870.28 (–2526.90–786.34)	0.3040
Ticagrelor (n, %)		
No	Reference	
Yes	–2681.06 (–4369.93– –992.20)	0.0020
ACEI/ARB (n, %)		
No	Reference	
Yes	–2720.06 (–4452.61– –987.51)	0.0023
β-blocker (n, %)		
No	Reference	
Yes	–473.17 (–2391.08–1444.74)	0.6291
CCB		
No	Reference	
Yes	357.07 (–1370.26–2084.41)	0.6856
Diuretic (n, %)		
No	Reference	
Yes	6152.57 (4687.14–7618.01)	<0.0001
Uric acid (μmol/L)	16.08 (10.48–21.68)	<0.0001
Fasting blood sugar (mmol/L)	164.06 (–178.71–506.84)	0.3490
2–hour postprandial blood glucose (mmol/L)	–4.78 (–246.43–236.86)	0.9691

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Table 2 continued. Univariate analysis of the associations with serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

	NT-ProBNP	
	OR (95% CI)	P-value
Glycosylated hemoglobin (%)	0.14 (–556.97–557.24)	0.9996
Cystatin C		
Q1	Reference	
Q2	157.28 (–1932.17–2246.73)	0.8828
Q3	2242.92 (173.10–4312.73)	0.0345
Q4	8055.23 (5965.78–10144.68)	<0.0001

OR – odds ratio; CI – confidence interval. Study groups according to cystatin C levels: Q1, 0.49–0.83 mg/L; Q2, 0.84–1.04 mg/L; Q3, 1.05–1.38 mg/L; Q4, 1.39–4.21 mg/L. SBP – systolic blood pressure; DBP – diastolic blood pressure; PCI – percutaneous coronary intervention; CABG – coronary artery bypass surgery; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor antagonist; CCB – calcium channel blocker.

Table 3. Multivariate analysis of cystatin C and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Exposure	Non-adjusted		Adjust I model		Adjust II model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Q1	Reference		Reference		Reference	
Q2	157.28 (–1932.17–2246.73)	0.8828	78.74 (–1882.76–2040.25)	0.9373	–260.98 (–2268.21–1746.25)	0.7991
Q3	2242.92 (173.10–4312.73)	0.0345	604.38 (–1378.63–2587.40)	0.5508	531.23 (–1559.07–2621.53)	0.6189
Q4	8055.23 (5965.78–10144.68)	<0.0001	6727.24 (4599.70–8854.77)	<0.0001	5163.41 (2563.76–7763.05)	0.0001

OR – odds ratio; CI – confidence interval. Outcome variable: NT-ProBNP. Exposure Variable: Cystatin C. Non-adjusted model: none. Adjust I model adjusted for: weight, heart rate, aspirin, ticagrelor, angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist (ACEI/ARB) and diuretics. Adjust II model adjusted for: weight, heart rate, aspirin, ticagrelor, ACEI/ARB, diuretics and uric acid. Study groups according to cystatin C levels: Q1, 0.49–0.83 mg/L; Q2, 0.84–1.04 mg/L; Q3, 1.05–1.38 mg/L; Q4, 1.39–4.21 mg/L.

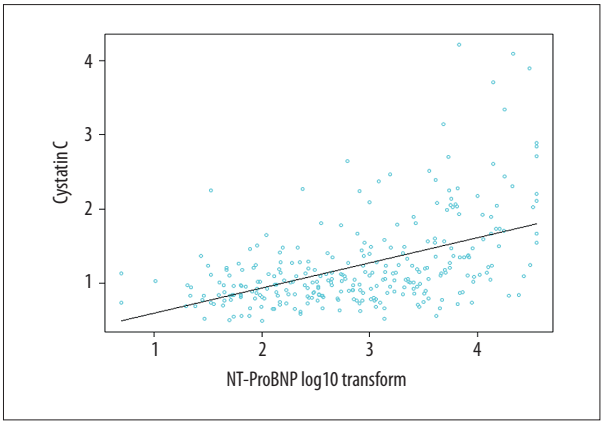

Figure 3. Pearson correlation analysis of cystatin C and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

between the levels of cystatin C and cardiac function, assessed using the New York Heart Association (NYHA) class I to IV criteria, and NT-proBNP levels in patients with UAP. The study findings also showed a significant association between levels of cystatin C and NT-ProBNP that remained after adjusting for potential confounding factors in the four study groups (Q2 *vs.* Q1: OR, –260.98; 95% CI, –2268.21–1746.25; Q3 *vs.* Q1: OR, 531.23; 95% CI, –1559.07–2621.53; Q4 *vs.* Q1: OR, 5163.41; 95% CI, 2563.76–7763.05). Pearson correlation analysis also confirmed a significant association between cystatin C and NT-ProBNP (r=0.4875; P<0.001).

Previous studies showed that inflammation is involved in the occurrence and development of atherosclerosis [30,31]. The pathogenesis of human atherosclerosis also involves degradation of the extracellular matrix (ECM) and vascular wall remodeling [33,34]. An increase or decrease in vascular wall remodeling can result in the accumulation of ECM, which is the basis of the pathogenesis of diseases that include tissue repair, inflammation, and fibrosis. Cystatin C is expressed in all nucleated cells and regulates the activity of cysteine protease, which is involved in the production and degradation of the ECM [35]. Also, cystatin C and its fragments may affect the phagocytosis and chemotaxis of granulocytes that participate in the inflammatory process [35].

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Recent studies have investigated the relationship between cystatin C and cardiovascular disease. In a study conducted in Finland, the predictive value of cystatin C in the diagnosis of non-ST segment elevation acute coronary syndrome (NSTE-ACS) in 245 patients who underwent one-year followed-up showed that the increase of cystatin C was an independent predictor of all-cause mortality and combined events in patients with NSTE-ACS [36]. A previously published study conducted in China examined the relationship between cystatin C levels and myocardial perfusion and recovery of cardiac function in patients with STEMI after primary percutaneous coronary intervention (PCI) [37]. Multivariate logistic regression analysis showed that the level of cystatin C was an independent predictor of angiographic reflow and heart failure (HF) at six-month follow-up [37]. The results of this previously published study showed that increased levels of cystatin C were independently associated with myocardial perfusion injury and reduced cardiac function [37].

In patients with chronic heart failure (CHF), previous studies have also investigated whether cystatin C levels can be used as a serological marker for glomerular filtration rate (GFR) and prognosis in patients with CHF. In a previously published study, the authors included 102 patients with CHF and followed them for 24 months [38]. The results showed that cystatin C was an improved predictor of glomerular filtration rate (GFR) [38]. Serum cystatin C was an independent predictor of prognosis (HR=2.27 per SD increase; 95% CI 1.12–4.63) [38]. Also, the accurate early diagnosis of acute kidney injury (AKI) in patients with acute heart failure (AHF) can be a clinical problem, and cystatin C may contribute to the early diagnosis of AKI [39]. In a study that included 207 patients with AHF and used AKI as the main indicator and long-term mortality as the secondary indicator, the results showed that increased cystatin C could not be used as a marker for early diagnosis of AKI in AHF patients, but it could be used to predict the long-term prognosis of AHF patients ((HR=1.41; 95% CI 1.02–1.95) [39]. However, Cantinotti et al. also investigated the prognostic role of cystatin C after cardiac surgery in 248 children, and showed that at a median follow-up of 6.5 months, cystatin C was an early biomarker of AKI [40]. The findings from the present study showed a relationship between cystatin C, cardiac function, and NT-ProBNP in patients with UAP. These findings are consistent with the findings from previous studies that showed that increased levels of cystatin C were associated with reduced cardiac function and increased levels of NT-ProBNP, suggesting that cystatin C might be used to evaluate cardiac function.

Inflammation is involved in the occurrence and development of atherosclerosis [41,42]. The stimulation of inflammatory mediators promotes the secretion of cathepsin S and protease K by vascular smooth muscle cells, which leads to the overexpression of cysteine proteases and promotes degradation of elastic tissue. Cystatin C can inhibit some cysteine proteases, especially cathepsins. When the metabolism of cystatin C is imbalanced, this may result in pathological changes, and it is currently believed that cystatin C plays an important role in arterial wall proteolysis and anti-proteolytic activity, and participates in vascular wall ECM remodeling [43]. However, disorders of vascular wall remodeling are important in the pathogenesis of atherosclerosis, plaque rupture, and restenosis, which might explain why increased levels of cystatin C are associated with cardiovascular risk and prognosis.

This study had several strengths, including the identification of the correlation between levels of cystatin C, cardiac function, and NT-ProBNP in patients with UAP. Increased levels of cystatin C were associated with poor cardiac function and increased NT-ProBNP, which suggested that cystatin C may be a new serological marker of cardiac function in this group of patients. Serological testing for cystatin C costs less than the test for NT-ProBNP, which may be a factor that might increase its clinical use. In the present study, multivariate regression analysis was used to control for potential confounding influencing factors, which may have increased the reliability of the findings. However, this study had several limitations. The study was a cross-sectional observational study and was uncontrolled, and there may have been selection bias. The study was also conducted at a single center where the study investigators were also the clinicians who diagnosed and managed the patients. This study included a Chinese patient population, and whether the results of this study apply to other countries and ethnic groups remains to be confirmed by further studies.

Conclusions

This study aimed to investigate the association between serum levels of cystatin C, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and cardiac function in patients with unstable angina pectoris (UAP). Increased serum levels of cystatin C were associated with poor cardiac function, according to the New York Heart Association (NYHA) class I to IV criteria, and increased levels of NT-ProBNP in patients with UAP. The findings from this study, in a single center in China, support the need for further international large-scale clinical studies to evaluate the role of cystatin C and NT-ProBNP as diagnostic and prognostic markers in patients with UAP.

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