Journal of Cardiothoracic Surgery

RESEARCH

Open Access

Serum cystatin C predicts the risk of non-ST-elevation acute coronary syndrome

Hao Dong[1†], Dongping Xiao[2†] and Yong Tang[1*]

Abstract

Objective Inflammation markers have been proposed as the predictors of adverse cardiac events in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). This study aimed to investigate prognostic value of serum cystatin C (Cys-C) for NSTE-ACS patients.

Methods Cys-C, neutrophil to lymphocyte ratio (NLR) and high-sensitivity C-reactive protein (hsCRP) were examined in 212 NSTE-ACS patients and 60 controls. Global registry of acute coronary events (GRACE) score and major adverse cardiac events (MACE) in NSTE-ACS patients were recorded.

Results Cys-C level in the serum was significantly higher in NSTE-ACS patients than in control, and was positively correlated with hsCRP level and NLR as well as GRACE score at admission and 6 months after discharge in NSTE-ACS patients. Serum Cys-C level was identified as a new predictor of MACE.

Conclusion Serum Cys-C level may be an inflammation biomarker in patients with NSTE-ACS, and could be used as an independent predictor of MACE.

Keywords Non-ST-elevation acute coronary syndrome, Cystatin C, Inflammation, Biomarker

Introduction

Coronary artery disease (CAD) is a main cause of morbidity and mortality, and non-ST-elevation acute coronary syndrome (NSTE-ACS) is a common manifestation of CAD. During NSTE-ACS, atherosclerotic plaque initiates pathological processes, reduces coronary arterial blood supply and causes myocardial ischemia [1]. Global registry of acute coronary events (GRACE) score has been recommended to evaluate adverse outcomes in patients with acute coronary syndrome, and high GRACE score will increase the risk of death and help early intervention for high-risk patients to improve their prognosis [2].

Recent studies have shown that serum cystatin C (Cys-C) is closely associated with CAD [3, 4]. Cys-C was an independent predictor of cardiac events, and could be an indicator of CAD severity [5, 6]. Cys-C is also associated with an increased risk of death and could be used to predict major adverse cardiac events in patients with NSTE-ACS [7].

However, the relationship between serum Cys-C level and inflammation marker in NSTE-ACS patients is still unclear [8]. Therefore, in this study we aimed to analyze the relationship between Cys-C and inflammation marker in NST-ACS patients and evaluate the use of serum Cys-C level for early risk stratification of NST-ACS.

Patients and methods

Patients

This prospective study was approved by Ethics Committee of Nanjing University of Chinese Medicine (Approval

†Hao Dong and Dongping Xiao contributed equally to this study.

*Correspondence:
Yong Tang
fsyy01801@njucm.edu.cn
[1] Department of Cardiology, The Second Hospital of Nanjing, Nanjing University of Chinese Medicine, Nanjing 210000, China
[2] Department of Cardiology, The First Hospital of Nanchang, Nanchang 330000, China

No. 32,130) and all patients provided informed consent. This study recruited 212 NSTE-ACS patients (64.22 ± 14.35 years old) and 60 control participants (63.64 ± 8.01 years old) who proceeded coronary angiography to exclusive diagnosis of coronary heart disease. The two groups were recruited consecutively from January 2015 to May 2016 and matched for the age and gender. The inclusion criteria for NSTE-ACS group were: diagnosed as NSTE-ACS according to Guidelines for the diagnosis and treatment of NSTE-ACS; had complete medical data including history of disease and clinical and biochemical tests; willing to cooperate for follow-up. The exclusion criteria for NSTE-ACS group were: the patients had other heart diseases such as myocarditis diagnosed by magnetic resonance imaging, severe inflammatory diseases, serious hepatic and renal failure, anemia or cancer.

All patients were evaluated for routine blood examination, electrocardiogram and routine clinical laboratory tests, including the liver and kidney function tests, troponin and brain natriuretic peptide (BNP), total plasma cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), creatinine (Cr), low density lipoprotein cholesterol (LDL-C), high-sensitivity C-reactive protein and Cys-C. Global registry of acute coronary events (GRACE) score were calculated from eight variables as described previously [9].

Follow-up

Major Adverse Cardiac Events (MACE) were recorded for each patient during the follow-up of three months, including cardiac shock, recurrent myocardial infarction and angina, heart failure and any cause of death,

Statistical analysis

Normally distributed data were presented as mean ± standard deviation. Abnormally distributed data were presented as median. All data were analyzed using SPSS version 17.0 (SPSS Inc, Chicago, IL, USA). Normally distributed data were compared by student *t* test and abnormally distributed data were compared by Wilcoxon test. Categorical variables were compared by Chi-square test. The relationship of indexes was analyzed by Pearson correlation analysis. A receiver operating characteristic (ROC) curve analysis was performed to calculate optimal cut-off value of Cys C for predicting MACE. $P < 0.05$ indicated statistical significance.

Results

Baseline characteristics of the subjects

We consecutively recruited 500 patients and 250 controls who proceeded coronary angiography to exclusive diagnosis of coronary heart disease. Finally, we included 212 patients and 60 control in NSTE-ACS and control groups, respectively. Among 212 patients in NSTE-ACS group, they were further qualified into unstable angina and non-ST elevation MI (NSTE-MI) according to troponin levels. About 98 patients (46.2%) were diagnosed as NSTE-MI. Baseline characteristics of the patients in NSTE-ACS and control groups showed no significant difference including the age and gender (Table 1).

Association of serum Cys-C level with characteristics of NSTE-ACS patients

As shown in Table 1, NSTE-ACS group and control group showed significant difference in serum Cys-C level (0.94 ± 0.28 vs. 0.76 ± 0.12 mg/L, $P = 0.00$). In addition, the two groups showed significance differences in hsCRP and NLR.

Among 212 NSTE-ACS patients, 135 patients (63.7%) received revascularization procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) after admission. Serum Cys-C level showed positive correlation with GRACE score at admission and six months after discharge ($r = 0.322$, $P = 0.030$ and $r = 0.394$, $P = 0.002$, respectively). Serum Cys-C level also showed positive correlation with hsCRP and NLR ($r = 0.404$, $P = 0.000$ and $r = 0.323$, $P = 0.003$,

Table 1 Baseline characteristics of NSTE-ACS patient and control groups

	NSTE-ACS group n = 212		Control group n = 60	*P*
Age, years	64.23 ± 14.34	63.64 ± 8.01		0.83
Male gender, n (%)	133 (62.74)	37 (61.67)		0.88
Smoking, n (%)	75 (35.38)	20 (33.33)		0.77
Hypertension, n (%)	105 (49.53)	29 (48.33)		0.87
Diabetes, n (%)	40 (18.87)	15 (25.00)		0.30
BMI, kg/m^2	25.35 ± 5.36	24.33 ± 2.81		0.40
Cr, umol/L	65.59 ± 14.78	63.53 ± 17.74		0.57
TC, mmol/L	4.53 ± 1.25	4.51 ± 1.08		0.95
TG, mmol/L	1.44 ± 0.85	1.37 ± 0.64		0.67
HDL-C, mmol/L	1.23 ± 0.32	1.27 ± 0.22		0.46
LDL-C, mmol/L	3.29 ± 0.99	3.07 ± 0.66		0.25
hs-CRP, mg/L[#]	10.40	0.47 (0.16,0.85)		0.00 *
NLR[#]	(6.63,26.20)	1.45 (1.21,1.92)		0.00 *
Admission GRACE score	5.03	-		-
Discharge GRACE score	(3.47,9.56)	-		-
Cys-C, mg/L	143.74 ± 44.94 111.32 ± 30.78 0.94 ± 0.28	0.76 ± 0.12		0.00*

Value are mean ± SD except where expressed as median (quartile 1, quartile 3)[#].
*$P < 0.05$ compared to control group. *NSTE-ACS* Non-ST-elevation acute coronary syndrome; *BMI* Body mass index; *TC* Total plasma cholesterol; *TG* Triglycerides; *HDL-C* High density lipoprotein cholesterol; *LDL-C* Low density lipoprotein cholesterol; *hsCRP* High-sensitivity C-reactive protein; *NLR* Neutrophil to lymphocyte ratio; *GRACE* Global registry of acute coronary events; *Cys-c* Cystatin c

Table 2 Logistic regression analysis of the factors predicting MACE in NSTE-ACS patients

Variables	OR	95% CI	*P* value
Cystatin C	8.271	2.670z–25.624	< 0.001
Age	1.050	1.025–1.076	< 0.001
Triglycerides	0.647	0.448–0.936	0.02

OR: odds ratio, 95% CI 95% Confidence interval

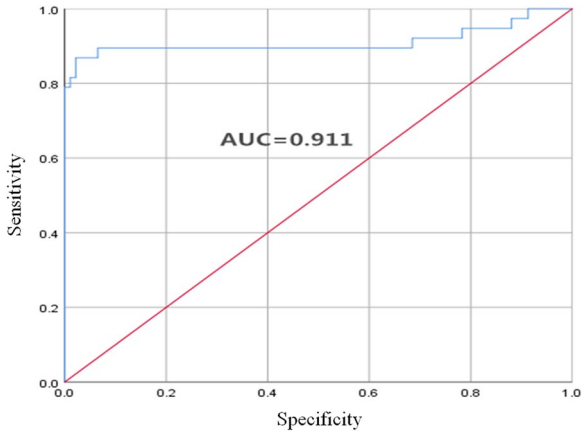

Fig. 1 ROC curve analysis of the predication of MACE based on serum CHI3L1 level. Area under the curve (AUC) was 0.911

respectively), and the age and Cr ($r=0.443$, $P=0.000$ and $r=0.662$, $P=0.000$, respectively). However, serum Cys-C level was not correlated significantly with TG, TC, LDL-C and HDL-C.

Serum Cys-C level predicts MACE

Logistic regression analysis using single factor showed that Cys-C [odds ratio (OR) 8.271, 95% confidence interval (CI) 2.670-25.624, $P<0.001$], age (OR 1.050, 95% CI 1.025–1.076, $P<0.001$), and TG (OR 0.647, 95% CI 0.448–0.936, $P=0.02$) could be independent predictors of MACE (Table 2). Logistic regression analysis using multiple factors showed that Cys-C (OR 5.403, 95% CI 1.203–24.253, $P=0.03$) could be an independent predictor of MACE. ROC curve analysis showed that for serum Cys-C level at cutoff value of 0.9 mg/L, the sensitivity was 86.1% and the specificity was 96.8% (Fig. 1).

Discussion

In this study, we demonstrated significantly higher serum Cys-C level in NSTE-ACS patients compared to controls. In addition, serum level of Cys-C was correlated with GRACE score at admission and after discharge in NSTE-ACS patients, and was also correlated with inflammation markers such as hsCRP and NLR. Finally, we identified Cys-C as an independent predictor of MACE.

Cys-C is an inhibitor of cysteine protease. Compared with the creatinine and urea nitrogen, Cys-C is less likely to be affected by gender, age, diet and other factors. The kidney is the only organ that eliminates serum Cys-C, thus serum Cys-C plays important role in early evaluation of renal insufficiency [10].

Serum Cys-C could predict the risk of heart failure, stroke and death in high-risk populations [3–5]. Cys-C may be involved in the pathogenesis of CAD by several mechanisms: (1) Cys-C could adjust the activity of cysteine protease, thus maintain dynamic balance of extracellular matrix, which is involved in the pathogenesis of CAD [11]. (2) Cys-C is actively involved in matrix remodeling associated with plaque regression, and the level of cystatin C is positively correlated with plaque area [12]. (3) During Cys-C oxidation, free radicals are generated to increase the formation of foam cells and induce artery luminal stenosis, leading to artery luminal stenosis. Cys-C also promotes the proliferation and migration of vascular smooth muscle cells [13, 14].

In this study we found that serum Cys-C level was high in NSTE-ACS patients. In addition, logistic regression analysis showed that serum Cys C level was the independent predictor of MACE, consistent with previous study [6]. Notably, we confirmed that Cys-C serum level was correlated with inflammation markers hsCRP and NLR, which are involved in coronary heart disease [15]. These findings suggest that Cys-C could affect the phagocytosis and chemotactic function of granulocyte, and participate in the process of inflammation to promote the pathogenesis of CAD.

Due to the high mortality and poor prognosis of NSTE-ACS, early risk stratification is essential to patients with NSTE-ACS. Various scoring systems have been developed for prognostic and risk stratification of NSTE-ACS patients. AHA and ESC guidelines emphasize the significance of GRACE score, and recommend it for routine use [3]. In-hospital GRACE score > 140 is considered as increased risk of mortality. In addition, recent studies have proposed a variety of parameters to predict the outcomes of ACS patients [16–19]. In this study, we found that serum Cys-C level was correlated positively with GRACE score at admission and after discharge, indicating that serum Cys-C level may be used for early risk stratification. Early detection and treatment of NSTE-ACS patients with high Cys-C level in the serum may improve the prognosis and reduce the mortality.

This study has several limitations. First, this study is a single-center observational study with possible bias for patient selection. Second, the sample size is relatively small. Third, we only measured several laboratory parameters and did not detect other parameters such as serum

cortisol level [20]. Further large-scale multiple-center studies are needed to confirm our conclusion.

In conclusion, serum Cys-C may be involved in the progression of NSTE-ACS and become a useful biomarker of inflammation. Detection of serum Cys-C level may help early risk stratification to predict the prognosis of NSTE-ACS patients.

Author contributions

HD and DX collected and analyzed the data. YT designed the study. All authors wrote and approved the manuscript.

Funding

This study did not receive funding.

Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This prospective study was approved by Ethics Committee of Nanjing University of Chinese Medicine (Approval No. 32130) and all patients provided informed consent.

Competing interests

The authors declare that they have no competing interests.

Received: 3 May 2023 Accepted: 21 November 2023
Published online: 01 December 2023

References

1. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Jneid H, Ettinger SM, Ganiats TG, Philippides GJ, Jacobs AK, Halperin JL, Albert NM, Creager MA, DeMets D, Guyton RA, Kushner FG, Ohman EM, Stevenson W, Yancy CW. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patientswith unstable angina/non-ST-elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2013;61:e179-347.
2. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, ESC Committee for Practice Guidelines. ESC Committee for Practice Guidelines ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999–3054.
3. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med. 2005;352:2049–60.
4. Arpegård J, Magnusson PK, Chen X, Ridefelt P, Pedersen NL, De Faire U, Svensson P. Cystatin C predicts incident Cardiovascular Disease in twins. J Am Heart Assoc. 2016;5(6):e003085.
5. Taglieri N, Fernandez-Berges DJ, Koenig W, Consuegra-Sanchez L, Fernandez JM, Robles NR, Sánchez PL, Beiras AC, Orbe PM, Kaski JC. SIESTA investigators. Plasma cystatin C for prediction of 1-year cardiac events in Mediterranean patients with non-ST elevation acute coronary syndrome. Atherosclerosis. 2010;209:300–5.
6. Kiyosue A, Hirata Y, Ando J, Fujita H, Morita T, Takahashi M, Nagata D, Kohro T, Imai Y, Nagai R. Plasma cystatin C concentration reflects the severity of coronary artery Disease in patients without chronic Kidney Disease. Cric J. 2010;74:2441–7.
7. Ristiniemi N, Lund J, Tertti R, Christensson A, Ilva T, Porela P, Pulkki K, Pettersson K. Cystatin C as a predictor of all-cause mortality and Myocardial Infarction in patients with non-ST-elevation acute coronary syndrome. Clin Biochem. 2012;45:535–40.
8. De Servi S, Mariani G, Piatti L, Leoncini M, Rubartelli P, Pitì A, Curello S, Galdangelo F, Vandoni P, Rossetti E, Mariani M, Boschetti E, Re G, Loznicker M. Time course changes of cystatin C and inflammatory and biochemical markers in non-ST-elevation acute coronary syndromes. J Cardiovasc Med (Hagerstown). 2014;15:42–7.
9. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and Myocardial Infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333:1091.
10. Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey AS, Gansevoort RT, CKD Prognosis Consortium. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013;369:932–43.
11. Bengtsson E, To F, Grubb A, Håkansson K, Wittgren L, Nilsson J, Jovinge S. Absence of the protease inhibitor cystatin C in inflammatory cells results in larger plaque area in plaque regression of apoe-deficient mice. Atherosclerosis. 2005;180:45–53.
12. Gu FF, Lu SZ, Chen YD, Zhou YJ, Song XT, Jin ZN, Liu H. Relationship between plasma cathepsin S and cystatin C levels and coronary plaque morphology of mild to moderate lesions: an in vivo study using intravascular ultrasound. Chin Med J (Engl). 2009;122:2820–6.
13. Longenecker CT, Hileman CO, Funderburg NT, McComsey GA. Rosuvastatin preserves renal function and lowers cystatin C in HIV-infected subjects on antiretroviral therapy: the SATURN-HIV trial. Clin Infect Dis. 2014;59:1148–56.
14. Picchio V, Pagano F, Chimenti I. Cardiac stromal cells on stage: from dull filler to specialized actors. Biocell. 2022;46(8):1875–7.
15. Moreira DM, da Silva RL, Vieira JL, Fattah T, Lueneberg ME, Gottschall CA. Role of vascular inflammation in coronary artery Disease: potential of anti-inflammatory Drugs in the prevention of atherothrombosis. Inflammation and anti-inflammatory Drugs in coronary artery Disease. Am J Cardiovasc Drugs. 2015;15:1–11.
16. Aydınyılmaz F, Sunman H, Algül E, Özkaya İbiş AÖ, Özbeyaz NB, Guliyev İ, Erzurum M, Çimen T, Tulmaç M. The effect of ticagrelor and clopidogrel on angiographic parameters according to diabetic status in patients with ST elevation Myocardial Infarction. Russian J Cardiol. 2022;27(9):5021.
17. Bhat R-A, Ali S-M, Hussenbocus Y-a-a-M, Rathi A, Bhat J-A, Khan A-A, et al. Use of Impella cardiac axial flow pump for cardiogenic shock (a newer alternative)–How good is the evidence? Biocell. 2022;46(5):1139–50.
18. Algül E, Özbeyaz NB, Şahan HF, Aydınyılmaz F, Sunman H, Tulmaç M. Stress hyperglycemia ratio is Associated with high Thrombus burden in patients with Acute Coronary Syndrome. Angiology. 2023. https://doi.org/10.1177/00033197231167054.
19. Ozbeyaz NB, Gokalp G, Algul E, Sahan HF, Aydinyilmaz F, Guliyev I, Kalkan K. H2FPEF score and contrast-Induced Nephropathy in patients with Acute Coronary Syndrome undergoing percutaneous coronary intervention. Angiology. 2023;74(2):181–8.
20. Dikme O, Dikme O. Serum cortisol level as a useful predictor of surgical Disease in patients with acute abdominal pain. Signa Vitae. 2019;15:27–31.

Publisher's Note