Cystatin-C in patients with acute coronary syndrome: Correlation with ventricular dysfunction, and affected coronary vessels

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Objective   This study is designed to inspect the circulating levels of cystatin C (Cy/C) in patients with acute coronary syndrome (ACS) and to evaluate the association of Cy/C levels with ejection fraction and angiographic number of stenosed coronaries.

Methods   136 participants with ACS were enrolled in this case–control survey and compared with 94 control. Hematological assessments were done for all the participants and included Cy/C, creatinine, and uric acid were measured using conventional techniques. Creatinine clearance rate was calculated and estimated glomerular-filtration-rate (eGFR) were measured. Echocardiographic assessment of ejection fraction was done with a cut-off point <40 left ventricular ejection fraction% designated for LV systolic dysfunction. Angiographic evaluation involved in this study depending on the severity of stenosed coronaries by calculating number of arteries display not less than 1 critical stenosis (designed as >70% decrease in caliber).

Results   Ejection fraction was significantly lower in in ACS patients than control group (p < 0.05). Serum Cy/C was significantly higher in patients' group. The mean plasma uric acids values were significantly higher in patients' group (p-0.001) but with no significant differences in creatinine and creatinine clearance (p < 0.05) observed between groups. The eGFR were significantly lower in ACS people compared to healthy persons. Correlation studies of Cy/C showed positive correlation with serum creatinine and serum uric acid; as well as non-significant negative correlation with eGFR (p > 0.05).

Conclusion   Besides the role of Cy/C in early detection of renal dysfunction, it could have a role in diagnosis of ACS and evaluation of LV systolic dysfunction. Nevertheless, this study showed Cy/C was not related to the number of coronary arteries affected.

Keywords   cystatin C, acute coronary syndrome, left ventricular ejection fraction, coronary angiography.

Introduction

Cystatin-C (Cy/C) is an innovative biomarker of renal function, which seems to share even strong correlation with mortality and vascular risk over serum creatinine or estimated-glomerular filtration rate (eGFR) in aging and admitted acute coronary syndrome (ACS) subjects. Whether a high risk of coronary–vascular diseases related to elevated CyC is due to amplified ischemic load, raised risk of embolism, or another pathway is uncertain.[1–3] Cy/C is formed and released by cardiac cells, where its production is raised up during myocardial necrosis.[1]

Three clinical subtypes of ACS, involving unstable angina, and ST and non-ST segment elevation myocardial infarction (MI), are primary causes of mortality and debility universally.[2] The incremental role of Cy/C beyond conventional renal and cardiac markers leftovers moderately discovered.[4] Cy/C is not influenced by age, sex, race, and lean body mass and may be more suitable for sensing mild–moderate changes in eGFR.[5] A closer look at the recent data indicates that higher values of Cy/C in patients with ACS are associated with raised risk for cardiovascular events and death independent of renal function.[6]

This study is designed to inspect the circulating levels of Cy/C in patients with ACS and to evaluate the association of Cy/C levels with ejection fraction and an angiographic number of stenosed coronaries.

Materials and Methods

This is a single-center study, patients were recruited from Shahid al-Mihrab Center for interventional cardiology; all had prearranged admission for diagnostic or therapeutic catheterization.

Study Participants

Patients were diagnosed as pure ACS (n = 136) only without other cardiac pathologies by a cardiologist and referred for further interventional catheterization. Sex and age well-matched healthy controls (n = 94) were selected as being free of any cardiological disabilities or any renal impairment. Body mass index (BMI), smoking habits, and history of diabetes mellitus and hypertension were also included in the study.

Description of ACS

Entire ACS patients met the diagnostic standards established by the 2014 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for managing non-ST-segment elevation ACSs and the 2013 ACC Foundation/AHA guideline for the management of ST-segment elevation MI.[1]

Quartiles of Cystatin-C in Study Subjects

We classified ACS patients into quartiles based on their blood Cy/C levels; <0.9, 0.9–1.49, 1.5–1.99, and >2.0 mg/L.[1] The

study population was stratified according to their levels of serum uric acid (SUA) at their first 6–12 h of admission, into two groups: first (<6.3 mg/dL), second (≥6.3 mg/dL).

Measurements of Other Biochemical Assays

All hematological assays were performed on the day of presentation on fasting blood which was drawn and stored at minus 70°C. Cy/C was measured by using Elabscience® Human Cy/C ELISA kit. While both creatinine and UA were measured using a conventional techniques. The creatinine clearance rate calculated using the Cockcroft–Gault formula in mL/min from plasma creatinine measured by mol/L as follows:[7]

$$Creatinine\ Clearance = \{(140 - Age) \times wt\ (kg) \times F\} / (Serum\ Creatinine * 0.8136)\ where\ F = 1\ for\ men,\ and\ 0.85\ for\ women$$

eGFR was measured by means of a new evaluation method established by adjusting of "Modification-of-Diet-in-Renal-Disease Study" formula, depending on information from "Chinese CKD" subjects:[8]

$$eGFR\ (ml/min\ per\ 1.73\ m2) = 175 \times Scr^{1.234} \times age^{-0.179};\ [Scr\ \text{-}mg/dl......and\ if\ female \times 0.742$$

25 subjects who had renal impairment defined as an eGFR<60, were omitted.

Echocardiographic Study

Standard echocardiographic examination was done at rest by means of a VIVID 9 apparatus (GE Healthcare®) with 2.5/3.5-MHz probe. A single qualified physician performed echocardiography. The left ventricular ejection fraction (LVEF%) measured by using "modified Simpson's technique". A cut-off point <40 LVEF% designated for expressing LV systolic dysfunction. Henceforth, ACS patients divided into two-sub-groups: EF <40% *vis* ≥40%.[9]

Coronary Angiography

At least, two-skillful angiographers inspected angiography images, whereas severity of stenosed coronaries evaluated by calculating number of arteries displays not <1 critical stenosis (designed as >70% decrease in caliber).

Biostatistics Assay

All statistics finalized with SPSS software, version 25. The ACS patients were clustered into quartiles based on their serum Cy/C levels. ANOVA was used for continuous covariates and chi-square for dichotomous variables. Comparisons of continuous data (given as means) were performed by means of *t*-tests for independent samples. Receiver operating characteristic (ROC) curve studies were performed to establish specificity/sensitivity. Univariate logistic regression analysis was done wherever required.

Ethical Consideration

A conversant consent at the commencement obtained from each participant (or family associate) for ACS subjects and controls individually, and our study final approval from the local committee for research ethics at University of Babylon. Arranged authorization for blood sampling, besides hospital approval by ethical committee of the entire work.

Results

Mean age of our ACS patients was 59.3 ± 13.1 years, which is not unlike the age of the control group. Similarly, BMI did not significantly differ between the two study groups. The males' number was 92 (67.7%), which were less significant than the control 83 (88.29%). The mean LVEF% was incomparable between the groups being lower in the ACS group, even though, the mean EF% of both study groups still were within the normal limits. The mean levels of creatinine and calculated creatinine clearance for ACS and control subjects were parallels mutually. The mean plasma UA values were significantly higher in the patients (*p*-0.001). Correspondingly, the estimated GFR was significantly lower in ACS people compared to healthy persons (109.6–127 ml/min per 1.73 m²), sequentially. A higher incidence of risk-factors in terms of concomitant hypertension and diabetes in ACS patients were significant (*p*-0.05). Serum Cy/C levels were significantly higher in cardiac patients (Table 1).

Table 1. **Baseline characteristics of the two groups involved in the study.**

Characteristics	Group	Number	Mean	Std. deviation	*P*-value
Age	1	136	59.3	13.1	>0.05
	2	94	51.9	12.1	
Male gender no (%)	1	138	92 (67.7)		0.05
	2	94	83 (88.29)		
BMI (kg/m²)	1	136	27.2	4.6	>0.05
	2	94	26.8	4.5	
Left ventricular EF%	1	129	50.5	10.7	0.05
	2	94	57	6.9	
Uric acid	1	136	5.9	1.8	0.001
	2	94	4.4	1.3	
Creatinine	1	136	0.8	0.4	>0.05
	2	94	.87	.11	
Creatinine clearance	1	129	73.7	60.5	>0.05
	2	94	73.9	15.8	
eGFR (mL/min/1.73 m²)	1	129	106.7	32.1	0.05
	2	76	127.9	27.8	
Cystatin-C (mg/L)	1	102	1.4	1.0	0.05
	2	94	0.50	.26	
Hypertension no (%)	1	136	74 (54.4)		0.05
	2	94			
Diabetes no (%)	1	136	60 (66.9)		0.05
	2	94	16 (16.8)		

eGFR, estimated glomerular filtration rate; EF, ejection fraction.
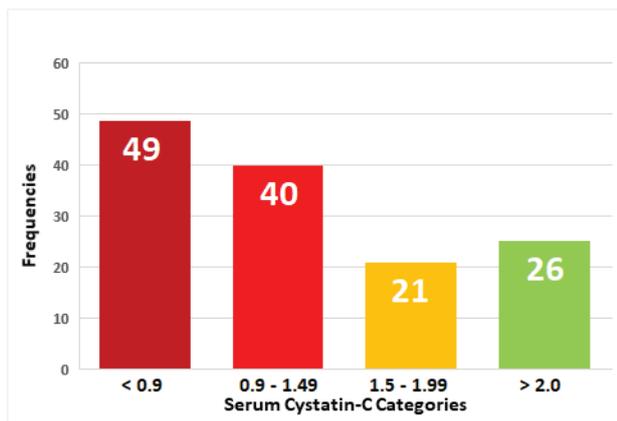
Fig. 1 **Frequency of cystatin-C (mg/L) quartiles among ACS patients.**

significant variation in the distribution of following variables according to Cy/C quartiles: creatinine, BMI, creatinine clearance, UA, eGFR, history of diabetes, hypertension, EF, and angiographic findings regarding the number of stenosed coronaries. Meanwhile, significant difference was observed concerning age, gender, and smoking practice. Linear regression analysis revealed positive weak significant association of Cy/C to creatinine, negative and no significant association of Cy/C to eGFR and positive significant association of Cy/C to SUA in ACS (Figs. 2A–C).

ROC study verified Cy/C 0.955 as a cut-off level to predict incidence of ACS. The sensitivity, specificity, and accuracy for Cy/C were 84, 86, and 84% sequentially, while the sensitivity, specificity, and accuracy of SUA were 58, 72, and 73% sequentially (Fig. 3). Patients were divided to 2 subgroups: high Cy/C group (≥0.95 mg/L) (n=61) and the low Cy/C (<0.95 mg/L) (n=75) was the second group.

The issue of classification of the subjects' levels of Cy/C into quartiles is well-exposed in Fig. 1, which showed that two-thirds of the patients had lower Cy/C values than those with higher values.

The distribution of the study variables according to Cy/C quartiles is demonstrated well in Table 2. There was no

Discussion

As a serious disorder, ACS remains a cause of high morbidity and mortality even with considerable therapeutic advances take into consideration risk assessment by using risk factors and risk biomarkers.[10] On top of out-of-date risk factors, some novel risk issues found to be associated with ACS.[11,12] Both[13,14]

Table 2. **Baseline characteristics divided into quartiles of Cystatin-C (mg/L)**

Characteristics		Cystatin-C quartiles (mg/L)				Total	P-value
		I (n = 49) <0.9	II (n = 40) 0.9-1.49	III (n = 21) 1.5-1.99	IV (n = 26) >2.0		
Age/years		54.9	57.4	62.8	62.6		<0.05
Body mass index(kg/m²)		27.2	28	26.2	26.8		>0.05
Gender	M(n/total)	29/49	19/40	16/21	24/26	88/136	<0.05
	F(n/total)	20/49	21/40	5/21	2/26	48/136	
Creatinine (mg/mL)		.79	.79	.97	.99		>0.05
Creatinine clearance		94.7	59.3	76.8	63.5		>0.05
Uric acid (mg/dL)	<6.3	19	15	11	8	53	>0.05
	≥6.3	11	10	2	8	31	
eGFR(mL/min/1.73m²)	<60	8/49	8/40	2/21	4/26	22/136	>0.05
	>60	41/49	32/40	19/21	22/26	114/136	
Smoking	Not smoker	25/49	14/40	5/21	7/26	51/136	<0.05
	Current-smoker	16/49	16/40	6/21	10/26	48/136	
	Ex-smoker	8/49	10/40	10/21	9/26	37/136	
History of diabetes		20/49	18/40	11/21	10/26	59/139	>0.05
History of hypertension		29/49	27/40	15/21	7/26	78/136	>0.05
Left ventricular ejection fraction	≥40%	8	2	4	4	18	>0.05
	<40%	21	21	9	11	62	
Angiography (number of stenosed-coronaries)	1-vessel	11/49	12/40	9/21	5/26	37/136	>0.05
	2-vessels	28/49	12/40	1/9	10/26	51/136	
	3-vessels	6/49	8/40	9/21	7/26	30/136	
	4-vessels	4/49	8/40	2/21	4/26	18/136	

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D. Ali Abed et al.
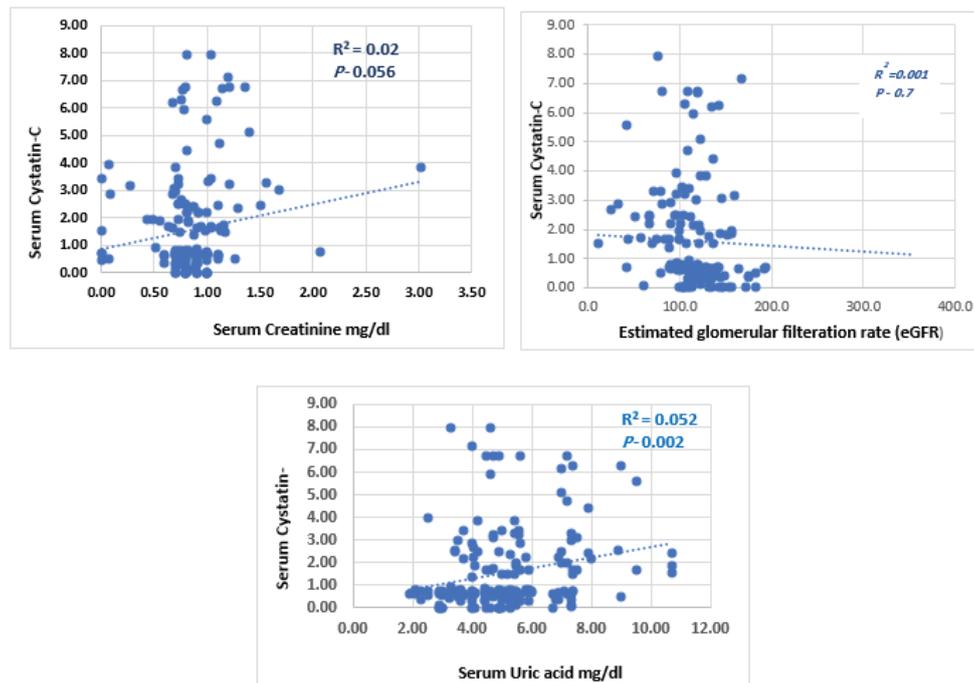Cystatin-C in patients with acute coronary syndrome

Fig. 2 **Scatter blot diagram of cystatin-C to creatinine, estimated glomerular filtration rate, and uric acid in ACS patients.**
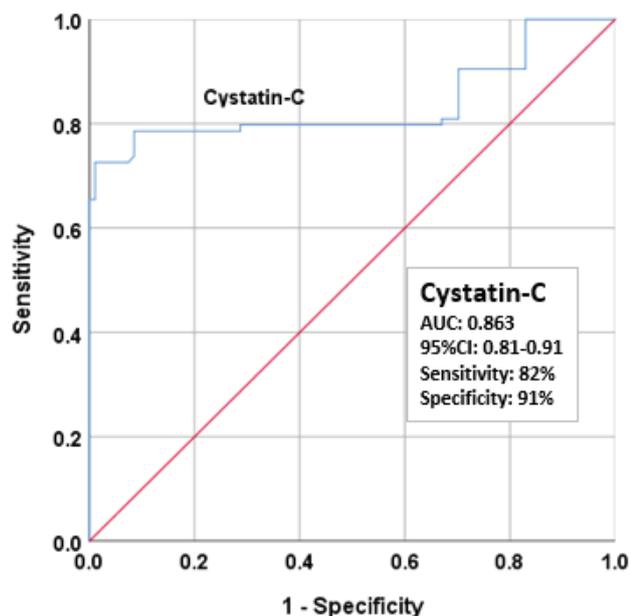

Fig. 3 **ROC curve for cystatin-C in acute coronary syndrome.**

found that Cy/C is less affected by factors like age, sex, and muscular mass over plasma creatinine and therefore might be a good biomarker of cardiovascular risk and cardiac impairment specially during aging. Their findings did not match our study findings of significant variances observed in Cy/C quartiles regarding age, sex, and smoking practice. Parikh et al. exposed independent association of high levels of Cy/C with risk issues like age, female sex, BMI, and smoking, even in people without chronic kidney diseases.[15]

In this study, Cy/C levels in patients and control groups were close to the references of other studies.[16,17] Cy/C was significantly higher in ACS group finding matches with other researches like Ge et al.[18] This high level of Cy/C could reflect

the atherotic changes in ACS subjects as Cy/C is expressed in all nucleating cells, controls action of "cysteine proteases." Cy/C and its fragments may influence the phagochemotactic ability of neutrophil, shares as well as regulates inflammatory responses. Inflammation contributes a vital role in the progression of atherosis. Thus, Cy/C might reflect amplified inflammation which subsidizes to vulnerable coronary-sclerotic plaque.[19]

Our result of a high level of Cy/C in ACS patients can document the role of Cy/C as a diagnostic biomarker, consistent to other studies like Eriksson et al.,[20] who concluded that Cy/C may reflect surely the existence or absence of ACS.

There is overwhelming evidence corroborating the notion that higher Cy/C values is correlated to a higher incidence of coronary–vascular events in symptomless elder peoples, and in cardiac failure. Yet, the reasons for such associations are indefinite.[21,22]

Tayeh et al.[23] assessed prognostic value of Cy/C to predict "major adverse cardiac events" in ACS. Therefore, Cy/C might be a valuable biomarker to diagnose coronary sclerosis. Other surveys proposed increased Cy/C levels might indicate elevated risk for heart disease/failure, stroke, in addition to mortality.[24] Meanwhile, close association of Cy/C and acute ischemic stroke was also published in another survey.[25]

The positive correlation of Cy/C with serum UA and creatinine observed in this work; are consistent with other analyses.[12,26] Harada et al.,[26] found that Cy/C had significant relations with both creatinine and SUA mutually in Japanian undergraduates and this concomitant "high Cy/C and SUA values" was related with subclinical lipids dysregulation and proposed the cardiometabolic risks. The negative correlation of Cy/C and eGFR in our study is in agreement with Shlipak et al,[21] who reported higher Cy/C levels which reflect early GFR problems. Further evidences supporting a graded association between high blood Cy/C levels and increased incidence of CVD in people with GFR ≥60 mL/min/1.73 m^2.[4,27]

The higher incidence of associated risk factors in term of concomitant hypertension and diabetes mellitus in ACS patients was significant, could be related to the finding of Muntner et al.[28] who displayed the incidence of risk-factors like tobacco-use, hypertension, besides others was higher in individuals with elevated Cy/C concentrations.

Lodh et al., used a cut-off Cy/C level of 1 mg/L and gained sensitivity of 77.8 for distinguishing ACS patients, nevertheless, the specificity was not much 62 and the area under the curve was 0.831 (29). In this study, the cut-off value used was 0.955, at a higher cut-off we obtained a lesser specificity. The sensitivity was 86, specificity was 84 and 86%, which indicates the predictive value of Cy/C as a biomarker for ACS and this agreed with Qing et al.[30] findings, who reported a modest predictive rate of Cy/C as a single biomarker for ACS.

Our study showed the association of higher Cy/C concentration (at the four quartiles) in ACS patients with lower systolic function of the left ventricle reflected by lower EF and this is inconsistent to other analysis like Shuaila et al., who found that higher Cy/C values associated with lower EF.[31] Same outcomes were reported by Moran et al.,[32] who revealed that Cy/C can be also a biomarker for cardiac failure. Tayeh et al also showed the association between higher Cy/C level and the lower EF. From this finding, we can conclude that Cy/C can detect the systolic dysfunction of the LV.[23]

Our data provide a convincing evidence that Cy/C level not related to the number of stenosed coronaries. Our finding was in contrast to other studies that showed that the Cy/C level have a tendency to increase with increment of diseased coronaries,[30,33] as well as Tayeh et al,[23] who found that patients with higher level of Cy/C (cut-off value 1.141 mg/L) had a significant high number of stenosed vessels in comparison to patients with lower Cy/C levels. The small sample size might explain these discrepancies. In ACS, the Cy/C was not related to the number of coronary arteries affected and this could be due to small size sample.

Conclusion

Cy/C is not only a good marker for early detection of renal impairment, but also could be a valuable biomarker for diagnosing coronary artery diseases, and Cy/C in patients with ACS is a powerful predictor of LV systolic dysfunction, assessing severity of the condition, and predict development of heart failure. It seems important to put factors like age, gender, and smoking habits into consideration during evaluation Cy/C level as our study showed it is affected by these factors.

Abbreviations

Cy/C – Cystatin C
ACS – Acute coronary syndrome
BMI – body mass index
eGFR – Estimated glomerular filtration
LVEF – Left ventricular ejection fraction
AMI – Acute myocardial infarction
SUA – Serum uric acid

Conflicts of Interest Disclosure

There are no conflicts of interest.

Competing Interests

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

The Institutional Review Board of the University of Babylon approved this study.

Author Contributions

All authors confirmed they have contributed to the intellectual content of this paper and have met the following three requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content, and (c) final approval of the published article. Ammar had an advisory role and a great cooperative effort for sample collection.

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