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ORIGINAL ARTICLE

Evaluation of Cystatin C as a biomarker of Severity of Coronary Artery Disease

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ABSTRACT

Background: Cystatin C has been associated with Coronary Artery Disease (CAD) even within normal ranges of Estimated glomerular filtration rate (eGFR) suggesting existence of GFR independent cystatin C mediated cardiovascular disease (CVD) risk. This study aimed to assess the relation between the biomarker and CV diseases. **Methods**: This is Case Control study which was conducted on 88 cases at departments of Medical Biochemistry and cardiac cath lab, Faculty of Medicine, Zagazig. Subjects enrolled in the study were divides into 2 groups: Group (I) included patients with CAD while Group (II) included healthy people with normal coronary artery. Every patient had a complete medical history taken, a routine clinical examination, laboratory testing, electrocardiography, coronary angiography and cystatin C assessment. **Results:** Compared to the control group, the cases group's serum cystatin C median levels increased in a statistically significant way. A statistically significant positive connection was seen between the Gensini score and the levels of TC, LDL, serum Cys-C and a positive significant correlation between serum Cys-C levels and both LDL and fasting blood glucose. ROC curve analysis was done during our study to show the values of cystatin C as a possible biomarker in CHD at (cut off =0.769), which had a sensitivity of 81.8% and a specificity of 69.1%, predictive values for positive (PVP) and negative (PVN) are 72%, 79%, and 75%, respectively, of accuracy. **Conclusion:** We concluded that high level of cystatin C is considered as an additional risk factor of coronary artery disease.
Keywords: Cystatin C, Coronary artery disease, Cardiovascular disease.

INTRODUCTION

Worldwide, coronary artery disease (CAD) is a common illness that has a significant negative impact on both health and the economy. Patients with coronary artery disease (CAD) have higher rates of morbidity and mortality when they have renal impairment. Patients with CAD are more susceptible to severe adverse cardiovascular events (MACEs) from even modest renal insufficiency [1]. A greater blood creatinine level and a lower estimated glomerular filtration rate (eGFR) are the two independent risk factors for MACEs. While the first description of human γ-trace, also known as post-γ-globulin, was published in 1961, the name Cystatin C was proposed in 1984 [2].

All nucleated cells consistently produce cyststatin c, also referred to as Cys C, a low molecular weight protein that inhibits cysteine protease, regardless of changes in the external and intracellular environments. Because it is eliminated by glomerular filtration, reabsorbed, and catabolized in proximal renal tubular cells without tubular secretion, this protein has all the characteristics of an ideal endogenous GFR marker [3].

Cystatin C as a viable biomarker for the assessment of early impaired renal dysfunction, mainly to distinguish between small reductions in GFR [4] **.** Elevated cystatin C is associated with a higher risk of cardiovascular disorders because it signals latent impaired renal function, which contributes to this increased risk. Even in cases when eGFR is within normal ranges, cystatin C has been associated with CVD in several investigations, suggesting that cystatin C may be a risk factor for CVD independent of GFR [5] **.**

Cystatin C is considered a protective protein due to its anti-atherogenic characteristics. It prevents the enzymatic cleavage of connective tissues and the degradation of extracellular matrix in the vasculature by inhibiting pro-inflammatory cathepsins. Curiously, cystatin C has been proposed as a useful biomarker for cardiovascular risk and has also been connected to mortality in a number of clinical settings [6]**.** This study aimed to assess the relation between the biomarker and CV diseases.

METHODS

This case-control study was performed on 88 cases who underwent coronary angiography and cystatin C assessment in the Departments of Medical Biochemistry and cardiac cath lab, Faculty of Medicine, Zagazig.

The study was approved by the Zagazig University local ethics commission (ZU-IRB # 10566). From all patients participating in this study, informed consent was obtained. The study follows the Helsinki Declaration, which is the World Medical Association's guideline of ethics for research involving human subjects.

Subjects enrolled in the study were divides into 2 groups; Group (I) included patients with CAD while Group (II) included healthy people with normal coronary artery.

Inclusion criteria:

Patients admitted to the catheterization lab for suspected or documented coronary artery disease and under gone coronary angiography and diagnosed to suffer from coronary heart disease with angiographic evidence of narrowing of one or more major coronary arteries greater than 50% of lumen stenosis. Control**;** age and sex matched people who attend outpatient clinics for routine care.

Exclusion criteria:

Patients with mental health problems, patients with physical disabilities, infectious diseases, lack of consent, chronic inflammatory disease other than atherosclerosis, patients on anti-inflammatory drugs as (NSAIFD & corticosteroid).

Every patient underwent a thorough physical and clinical examination as well as a full history taking, Electrocardiography 12 lead standard surface ECG to all patients. Coronary angiography seldinger technique with different views to check all segments of major coronary arteries. Gensini score assessment of severity of coronary artery disease. BMI (lean only).

Laboratory investigations

Fasting Blood sample; five ml (5ml) of peripheral venous blood samples was withdrawn from each subject under complete aseptic conditions and subdivided into 2 parts 1ml on fluoride for FBG o the remaining part was placed in plain tube for serum and Lipid profile. (TC, TG, HDL-C, LDL-C). Blood urea nitrogen (BUN), uric acid (UA).

Estimation of Cystatin C:

The kit measures the amount of Human cystatin C (Cys-C) in samples using an enzyme-linked immunosorbent assay (ELISA) that is sandwiched between two antibodies. After pre-coating the enzyme well with Human cystatin C(Cys-C) monoclonal antibody, add cystatin C(Cys-C) antibodies and incubate. Then, add biotin-labeled cystatin C(Cys-C) antibodies and mix them to create an immunological complex along with streptavidin-HRP. Repeatedly incubate and wash to eliminate any remaining uncombined enzyme. The liquid's color changes to blue after adding Chromogen Solutions A and B, and then the acid's action causes the liquid to finally turn yellow. A positive association was observed between the content of the human substance cystatin C (Cys-C) in the sample and the color chroma.

Last measurement: after adding the optical density (OD) at 450nm wavelength using the stop solution, treating the blank well as zero. This measurement needs to be completed within 15 minutes. get the linear regression equation for the standard curve derived from the standards' concentrations and corresponding OD values. The concentration of the linked sample can then be obtained by using the sample's OD values on the regression equation.

The curve was drawn as the standard curve on graph paper using the optical density (OD) value as the vertical and the standard density as the horizontal. Using the sample curve, find the associated density determined by the OD value of the sample; alternatively, use the sample OD value, standard density, and OD value to compute the standard curve's straight line regression equation.

STATISTICAL ANALYSIS

All of the data were collected, tabulated, and statistically analyzed using SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA). Quantitative data was expressed using the mean ± SD and median (interquartile range), whereas qualitative data was expressed using absolute frequencies (number) and relative frequencies (%). distinct samples The Student's t-test was used to compare two groups for variables that were regularly distributed, whereas the Mann Whitney U test was used for variables that were non-normally distributed. There were two sides to every test. P values were classified as statistically significant (S) if they were less than 0.05 and statistically insignificant (NS) if they were more than 0.05.

RESULTS

Table 1; demonstrates that there was no statistically significant difference in sex, age, or BMI between the two groups under study, indicating that the groups were matched. However, there was a statistically significant difference in smoking and hypertension between the two study groups and history of CAD as (22.7%) of cases were either hypertensive or had coronary artery diseases and half of them were smokers.

Table 2; demonstrated that a substantial positive association between the Gensini score and each of TC, LDL and serum Cys-C levels and a substantial positive connection between the levels of serum Cys-C and both LDL and fasting blood glucose.

Analysis by A ROC curve was created to display the cystatin C values as a possible biomarker in CHD at (cut off =0.769), which had a sensitivity of 81.8% and a specificity of 69.1%, 75% accuracy, 79% predictive value for negative (PVN) and 72% predictive value for positive (PVP) as shown in figure (1).

Table (3) demonstrates that no statistically significant difference according to sex existed between the groups under study HTN, history of CAD, BMI and smoking. On the other hand, there was an age difference that was statistically significant between the groups under investigation as 3rd tertile (Gensini score >38 points) group showed significant older age than other groups.

Table (4) related TG and HDL-C, although there was a statistically significant difference, there was no statistically significant difference between the tested groups related TC levels and LDL-C as 1st tertile (Gensini score <11 points) group showed higher average TC level readings. Additionally, compared to other groups, the third tertile (Gensini score >38 points) group had a statistically significant rise in LDL-C values.

Table (5) demonstrates that while for BUN, FBG, or creatinine, there was a statistically significant difference between the groups under study, but not for any other parameter.

For uric acid (UA) levels, with the 2nd tertile (Gensini score 11–38 points) group exhibiting higher mean values of UA levels. Additionally, the second tertile showed a statistically significant increase in UA levels (Gensini score 11-38 points) group when compared to 3rd tertile (Gensini score >38 points) group.

Table (6) demonstrates that, in comparison to other groups, the third tertile (Gensini score >38 points) group had a statistically significant rise in serum cystatin C mean levels, followed by Additionally, the 2nd tertile (Gensini score 11–38 points) group showed a statistically significant rise in UA levels compared to the 1st tertile (Gensini score <11 points) group.

Table (1): Demographic characteristics of the studied groups.

Variables			**Cases Group N=44**	**Control Group N=44**	**test**	**P value**
Sex	Male	N	28	25	0.427 (X^2)	0.513
		%	63.6%	56.8%		
	Female	N	16	19		
		%	36.4%	43.2%		
Smoking	No	N	22	8	8.547 (X^2)	**0.003***
		%	50.0%	18.2%		
	Yes	N	22	36		
		%	50.0%	81.8%		
HTN	No	N	34	4	41.684 (X^2)	**<0.001***
		%	77.3%	9.1%		
	Yes	N	10	40		
		%	22.7%	90.9%		
History of CAD	No	N	34	42	11.282 (X^2)	**0.013***
		%	77.3%	95.5%		
	Yes	N	10	2		
		%	22.7%	4.5%		
Age (years) Mean±SD			57.55±9.49	54.75±10.44	1.314 (t)	0.192
BMI Mean±SD			25.41±4.82	24.82±4.45	0.595 (t)	0.553

Independent t-Test (t), Chi square test (X^2) Coronary artery disease (CAD)

Table (2): Correlation analysis of serum Cystatin -C and Gensini score.

Variables		Gensini	Cystatin c
Gensini	**r**	1.000	.936**
	p	--------	0.000
Cystatin c	**r**	.936**	1.000
	p	0.000	---------
TC	**r**	.301*	.273
	p	.047	.073
TG	**r**	-0.027	0.001
	p	0.863	0.997
HDL	**r**	.076	.066
	p	.626	.670
LDL	**r**	.400**	.371*
	p	.007	.013
BUN	**r**	-0.235	-0.081
	p	0.125	0.600
FBG	**r**	-0.225	0.324*
	p	0.143	0.032
UA	**r**	-0.222	-0.177
	p	0.147	0.250
Creatinine	**r**	0.180	0.147
	p	0.242	0.340
BMI	**r**	0.121	0.106
	p	0.435	0.492

r= Correlation Coefficient, p= Sig. (2-tailed).

Table (3): Baseline demographic, and clinical characteristics based on the Gensini score tertiles.

Variables			1st tertile (Gensini score <11 points) Group N=10	2nd tertile (Gensini score 11-38 points) Group N=16	3rd tertile (Gensini score >38 points) Group N=18	test	P value
Sex	Male	N	8	12	8	4.915	0.086
		%	80.0%	75.0%	44.4%		
	Female	N	2	4	10		
		%	20.0%	25.0%	55.6%		
smoking	No	N	6	8	8	0.622	0.733
		%	60.0%	50.0%	44.4%		
	Yes	N	4	8	10		
		%	40.0%	50.0%	55.6%		
HTN	No	N	8	12	14	0.092	0.955
		%	80.0%	75.0%	77.8%		
	Yes	N	2	4	4		
		%	20.0%	25.0%	22.2%		
CAD	No	N	6	14	14	2.654	0.265
		%	60.0%	87.5%	77.8%		
	Yes	N	4	2	4		
		%	40.0%	12.5%	22.2%		

Age (years) Mean±SD	56.4±8.29 (46-67)	52±6.47 (42-60)	63.11±9.58 (45-79)	7.758 *(f)*	**0.001***	P1=0.195 P2=0.046 P3<0.001*
BMI Mean±SD	19.8±4.95 (16-29)	21.38±4.3 (16.9-28)	22.2±4.51 (16.5-28)	0.900 *(f)*	0.415	P1=0.394 P2=0.187 P3=0.599

(f) one way ANOVA
P1 =1st tertile group vs. 2nd tertile group.
P2 =1st tertile group vs. 3rd tertile group P3 = 2nd tertile group vs. 3rd tertile group.

Table (4): Lipid profile levels based on the Gensini score tertiles.

Variables	1st tertile (Gensini score <11 points) Group N=10	2nd tertile (Gensini score 11-38 points) Group N=16	3rd tertile (Gensini score >38 points) Group N=18	Test *(f)*	P value	Post hoc
TC Mean±SD Range	197.69±21.59 (172-243.2)	173.29±39.31 (125-240)	210.22±28.58 (135-250)	5.829	**0.006***	P1=**0.009*** P2=0.123 P3=0.034*
TG Mean±SD Range	134.34±38.52 (85.4-190)	115.38±31.48 (80.6-170)	120.16±42.66 (82.7-195)	0.790	0.460	P1=0.223 P2=0.349 P3=0.716
HDL-C Mean±SD Range	31.4±2.29 (29.2-35.2)	31.96±1.66 (30.3-35.1)	31.53±2.61 (28.4-36.3)	0.244	0.785	P1=0.535 P2=0.880 P3=0.579
LDL-C Mean±SD Range	109.17±27.17 (89-169)	117.43±27.52 (75.2-145)	141.97±19.26 (112-179.4)	7.243	**0.002***	P1=0.039* P2=0.810 P3=**0.042***

(f) One way ANOVA
total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)
P1 =1st tertile group vs. 2nd tertile group.
P2 =1st tertile group vs. 3rd tertile group
P3 = 2nd tertile group vs. 3rd tertile group.

Table (5): Laboratory investigations characteristics based on the Gensini score tertiles.

Variables	1st tertile (Gensini score <11 points) Group N=10	2nd tertile (Gensini score 11-38 points) Group N=16	3rd tertile (Gensini score >38 points) Group N=18	test	P value *(f)*	Post hoc
BUN Mean±SD range	17.58±4.52 (12.2-23.2)	18.53±4.48 (12.6-26.5)	15.33±3.25 (11.2-21)	2.793	0.073	P1=0.564 P2=0.165 P3=0.026*

Variables	1st tertile (Gensini score <11 points) Group N=10	2nd tertile (Gensini score 11-38 points) Group N=16	3rd tertile (Gensini score >38 points) Group N=18	test	P value *(f)*	Post hoc
FBG Mean±SD Range	118±22.23 (80-143)	118.5±25.59 (80-155)	111.78±17.11 (83-135)	0.485	0.619	P1=0.955 P2=0.471 P3=0.372
UA Mean±SD Range	4.9±1.78 (3-7)	6.1±1.4 (3-8)	4.21±0.62 (3.5-5.4)	9.740	**<0.001***	P1=0.022* P2=0.170 P3<0.001*
Creatinine Mean±SD Range	0.77±0.50 (0.21-1.59)	1.09±0.37 (0.64-1.71)	1.09±0.40 (0.69-1.81)	2.335	0.110	P1=0.199 P2=0.376 P3=0.616

(f) one way ANOVA
Blood urea nitrogen (BUN), uric acid (UA)
P1 =1st tertile group vs. 2nd tertile group.
P2 =1st tertile group vs. 3rd tertile group
P3 = 2nd tertile group vs. 3rd tertile group.

Table (6): Serum Cystatin c levels based on the Gensini score tertiles.

Variables	1st tertile (Gensini score <11 points) Group N=10	2nd tertile (Gensini score 11-38 points) Group N=16	3rd tertile (Gensini score >38 points) Group N=18	test	P value *(f)*	Post hoc
Cystatin c Mean±SD Range	4.08±1.81 (1.5-6.8)	11.04±2.16 (7.8-15.6)	15.16±3.56 (11.4-22)	51.351	<0.001*	P1<0.001* P2<0.001* P3<0.001*

(f) one way ANOVA
P1 =1st tertile group vs. 2nd tertile group.
P2 =1st tertile group vs. 3rd tertile group
P3 = 2nd tertile group vs. 3rd tertile group.

DISCUSSION

According to our research, the cases group's serum cystatin C median levels were statistically considerably more than the control group's. Between blood Cys-C levels, LDL, TC, and between serum Cys-C levels, both LDL, TC, the Gensini score and fasting blood glucose, a positive significant connection has been seen. In our work, we used the ROC curve analysis to display the values of cystatin C as a potential biomarker in CHD at (cut off =0.769), it demonstrated 75% accuracy, 72% predictive value for positive (PVP), 79% predictive value for negative (PVN), and 81.8% sensitivity and 69.1% specificity. In agreement with us, Koc *et al*. has demonstrated a significant relationship between low HDL, creatinine, homocysteine, and cystatin C in individuals with suspected CAD, as well as the existence or severity of CAD. But there wasn't much of a link between hs-CRP and cystatin C [7]. Numerous research directions have shown a connection between atherosclerotic vascular disease and renal impairment. According to Wang *et al*. CAD incidence and severity were linked to mild renal impairment, as indicated by high cystatin C; however, in this investigation,

creatinine and eGFR did not predict the development of CAD [8]. Our research supports the findings of Wang *et al*. and Koenig *et al*. that only cystatin C predicts the severity of CAD, while both are strongly and independently correlated with the prevalence of CAD among renal function markers. [8,9]. Additionally, there is no correlation between the presence or severity of CAD and serum creatinine, according to Koc *et al*., creatinine is not sensitive enough to identify minor abnormalities in renal function. Additionally, they discovered when compared to CRP, cystatin C is a more accurate and focused indicator of CAD [7].

In the same previously reported investigation, a cut-off value for cystatin C to indicate the presence of CAD has not yet been suggested. In their investigation, Koc *et al*. determined the ideal cystatin C cut-off value, which was found to be 0.82 mg/L with a 75.5% sensitivity and a 75% specificity, respectively [7].

In the same direction, Eriksson *et al*. revealed a correlation between higher CAD severity and a genetically dictated drop in Cys-C expression [10]. In the study of loew and colleagues reported that Polymorphism of cystatin c gene was found to be direct proportional with plasma concentration of cystatin c but not with prognosis of patients with CHD [11]. Niccoli *et al*. in agreement with earlier authors, showed that in patients with CAD and normal creatinine-derived GFR, increased blood cystatin C levels are associated with a persistent lesion pattern and independently predict the degree of coronary atherosclerotic load. According to this study, a higher coronary atherosclerotic burden may act as a mediating factor in the connection between the risk of cardiovascular events and cystatin C [12]. Salgado *et al*. concur with Niccoli *et al*. that decreased kidney function may be a mediating factor in the relationship between blood cystatin C levels and the degree and severity of CAD, since cystatin C is a more sensitive marker for GFR assessment than creatinine-based criteria [12, 13].

Given this information, Doganer *et al*. discovered that the dynamic physiology of cystatin C would vary based on whether CAD is a chronic or acute condition. For instance, increased levels of cystatin C may indicate acute coronary syndrome without ST-segment elevation, while decreased levels in a patient in clinical stability would indicate a more significant and stable atherosclerotic burden [14].

Only 10% of the control group showed elevated cystatin C levels, compared to 52% of the coronary artery disease cases that Thenmozhi investigated. For this data, a Pearson chi square analysis was performed, and the result was determined to be significant it suggests that levels of cystatin C and coronary artery disease are strongly correlated [15]. A study by Dandana *et al*. on the therapeutic efficacy of serum cystatin C predicting CAD in patients without CKD found that serum cystatin C levels can be a useful biochemical marker, predicting CAD and its severity [16]. Thenmozhi, in contrast, discovered no discernible connection between the levels of serum Cys-C and fasting blood glucose or LDL [15].

Lindholt *et al*. observation that individuals experiencing an ischemic coronary event had a considerably greater cystatin-C level than controls was therefore unexpected. Given that patients with aortic aneurysms exhibit a shortfall in cystatin-C, as evidenced by a drop in both plasma and arterial lesions, the protein appears to play a significant function in the artery wall. These aneurysms may have developed as a result of low cystatin-C levels that are unable to balance the increased production of cysteine proteases [17]. The reduction of cystatin-C, a significant protease inhibitor, may contribute to the start of an ischemic episode. Gao *et al*. sampled months or years prior to an ischemic incident, do not rule out the potential that cystatin-C expression falls in the atherosclerotic plaque prior to an ischemic event [6].

The higher plasma levels of cystatin-C in cases compared to controls contradict the results of the Albert *et al*. study, which found no relationship between cystatin-C and the risk of peripheral artery disease. This variation may result from a varied pathophysiology and rely on the atherosclerosis's location [18]. In reality, different variables predict different outcomes for distinct vascular beds, even if the same risk factors apply to both CAD and peripheral vascular disease. Peripheral artery disease is particularly sensitive to the effects of diabetes and cigarette smoking. Therefore, it is not surprising that CAD and peripheral disease have different risk markers [19]. Furthermore, the current results support the findings of Koenig *et al*., which showed a favorable association between cystatin-C and CAD incidence in a German cohort of participants enrolled in secondary prevention [9].

Wasyanto *et al*. suggest that the observed discrepancy between the decline in coronary plaque cystatin-C levels and the elevated plasma levels in individuals who experience subsequent coronary ischemic episodes may point to an excess of cystatin-C in vascular-dwelling cells, which could lead to a balance with decreased arterial expression [20]. Determining the significance of cystatin C measurement in predicting the existence and severity of coronary artery disease was the aim

of the Vakili *et al*. investigation. Additionally, the relationship between this biomarker and several metabolic components, such as blood sugar and lipid profile, was evaluated in order to ascertain the biomarker's function in metabolism. As a result, the relevance of the relationship was established. However, their research was unable to show how important it is for anticipating the degree of coronary artery disease [21].

Cystatin C levels were observed to be considerably lower in CAD patients by Doganer *et al*. It was significantly lower in individuals with considerable CAD compared to those with non-significant CAD and normal cases. The following were the blood levels of cystatin C and the number of coronary vessels affected (none, single-vessel, two-vessel, three-vessel, and four-vessel illness). The equivalent values are 1334.86±393.45, 801.67±418.70, 993.90±457.34, 744.09±354.53, and 682.30±294.43[14]. Furthermore, cystatin C level was found to be b=0.258, p<0.01) showed a strong correlation with the CAD severity score by Koc *et al*. The predicted incidence CAD cut-off value for cystatin C had a sensitivity and specificity of 75.5% at 0.82 mg/L and 75.0% [7].

The biochemical risk markers for atherosclerosis, including homocysteine, creatinine, and hs-CRP, were likewise positively correlated with the amount of cyclostatin C. Researchers investigated any possible links between cystatin C and CAD because of the strong correlation between cardiovascular disease and chronic renal disease and our increasing knowledge of the role Cystatin C plays in the onset of cardiovascular disease. Increased plasma levels of cystatin C have been associated with worse outcomes and risk stratification throughout the continuum of CAD [22].

Although Vakili *et al*.'s results did not support this notion, cystatin C may be a valuable laboratory marker in ordinary practice for predicting the presence and severity of CAD. This should be further investigated in future research [21].

Recommendations:

We present the most recent guidelines for the diagnosis and management of these patients, and we recommend considering the measurement of cystatin C as a method to diagnose patients with CAD at an early stage. In addition, further research needs to be done to examine this problem from every angle.

Declaration of interest:

The authors report no conflicts of interest.

Funding information:

This study was not supported by any source of finding.

CONCLUSION

We concluded that an early and accurate diagnosis should be the main goal of a physician treating CAD patients in order to prevent possibly damaging sequences. We also came to the conclusion that a high level of cystatin C is thought to be an extra coronary artery disease risk factor.

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