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Association of Cystatin C Levels with Cardiovascular Risk Factors in Patients with Acute Coronary Syndrome

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Abstract: Acute Coronary Syndrome (ACS) is a major health burden worldwide and causes more deaths and disability and incurs greater economic costs than any other illness in the world. Cystatin C is a naturally occurring protease inhibitor that protects the host tissue from cysteine proteases, which is a proatherogenic factor. Aim of our study was to assess the plasma Cystatin C concentration in patients hospitalized for ACS as there is very little literature available on the performance of Cystatin C in ACS patients of Indian population, and to investigate the relationship between Cystatin C and marker of renal function, eGFR. 100 cases presenting with ACS at our centre during study period were evaluated. The Pearson's Chi-Square test had used to demonstrate the associations of risk factors like diabetes mellitus, hypertension, history of ischemic heart disease and smoking history of acute coronary syndrome patients with their levels of plasma Cystatin C (≤0.95 and >0.95 milligram/liter). The plasma Cystatin C level of all studied patients of ACS was obtained in the range of 0.64 mg/L to 1.94 mg/L (1.19±0.22 mg/L). Cystatin C was found to be >0.95mg/L in 88% of the total population. Our study evidenced a significant association of Cystatin C level (>0.95mg/L) with eGFR ranges. Our study evidenced a significant association between Cystatin C >0.95 mg/L with diabetes and hypertension. Of the total smokers, 94.3% were found to have Cystatin C >0.95 mg/L. Our study evidenced a negative correlation between high Cystatin C (>0.95 mg/L) and HDL levels. The determination of Cystatin C at the time of hospitalization in patients with ACS may be a good clinical tool for cardiovascular risk stratification and clinical outcomes even in patients with preserved renal function.

Keywords: Atherosclerosis, Acute coronary artery disease, eGFR, Diabetes, Hypertension.

INTRODUCTION

Acute Coronary Syndrome (ACS) is a major health burden worldwide and causes more deaths and disability and incurs greater economic costs than any other illness in the world. It is also a leading cause of death in India, and its contribution to mortality is rising [1]. Genetic factors, a high-fat and energy-rich diet, hypertension, smoking, sedentary lifestyle, obesity, less exercise, insulin resistance and type 2 diabetes mellitus are the most powerful risk factors for ACS.

Basic and clinical research carried out in recent years has established a direct relationship between chronic kidney disease and cardiovascular disease [2, 3]. In daily clinical practice, serum creatinine concentrations and the glomerular filtration rate estimated with the Cockcroft-Gault formula [4] or Modification of Diet in Renal Disease equation [5] are commonly used to estimate renal function. However, plasma creatinine concentrations can be influenced by a number of factors, such as patient age, sex, muscle mass, physical activity, diet, and medication [6].

Cystatin C is a low molecular protein, synthesised by all nucleated cells is a naturally occurring protease inhibitor that protects the host tissue from cysteine proteases, which is a proatherogenic factor [7]. Cystatin C is a reliable marker of renal functions and its plasma concentration is dependent completely on GFR and emerged as a biomarker of cardiovascular risk. As Cystatin C concentrations are not influenced by age, sex, or protein ingestion, and being very sensitive to small changes in glomerular filtration, they are considered among the best markers of glomerular filtration status [8].

However, it is currently not known whether this relationship is due to the fact that Cystatin C is a better marker of renal function than serum creatinine or whether there are factors apart from glomerular filtration that affect the concentration of this protein and are additionally related to cardiovascular risk [9].

The association between elevated Cystatin C values and the development of cardiovascular complications in patients with coronary artery disease has been noted in various recents studied. Cystatin C levels in serum may denote myocardial tissue damage following ischemic events and can be a marker for cardiovascular morbidity and mortality [10].

Aim of our study was to assess the plasma Cystatin C concentration in patients hospitalized for ACS as there is very little literature available on the performance of Cystatin C in ACS patients of Indian population, and to investigate the relationship between Cystatin C and marker of renal function, eGFR.

MATERIALS & METHODS

This observational study was conducted at Sri Aurobindo Medical College & PG Institute, Indore over a period of 18 months from April 2016 to September 2017 among the patients admitted with ACS. 100 cases presenting with ACS at our centre during study period were evaluated. Patients with advanced kidney failure, suspected systemic inflammatory disease or major trauma were excluded from the study. A proper proforma for each patient was designed and filled which included demographic characteristics, presence of classic cardiovascular risk factors (diabetes mellitus, systemic hypertension, obesity and smoking), and history of known vascular disease (ischemic heart disease, cerebrovascular disease). Various investigations like CBC, Fasting Blood Sugar and 2 hr Post Prandial Sugar, Lipid Profile, serum creatinine, eGFR, Cystatin C, CPK MB, Trop T, Urine examination, Ultrasound abdomen, ECG, 2D-ECHO were also recorded in the proforma. Cystatin C was measured with an automated homogeneous immunoassay using a Dade-Behring BN ProSpec nephelometer.

Statistical Technique: The Pearson's Chi-Square test had used to demonstrate the associations of risk factors like diabetes mellitus, hypertension, history of ischemic heart disease and smoking history of acute coronary syndrome patients with their levels of plasma Cystatin C (≤0.95 and >0.95 milligram/liter).

RESULTS

A maximum of one hundred admitted patients of ACS were enrolled to observe the level of plasma Cystatin C. The age ranged from 25 to 85 years (mean ±SD 56.16±11.79), with 65 males and 35 of them being female. The plasma Cystatin C level of patients of ACS was obtained in the range of 0.64 mg/L to 1.94 mg/L (1.19±0.22 mg/L). Among the total, 69% of patients (n=69) presented with STEMI and 31% (n=31) with NSTEMI. Cystatin C was >0.95mg/L in 88% of the studied population. Our study evidenced a significant association of Cystatin C level (>0.95mg/L) with eGFR ranges. Cystatin was >0.95 in: 94.1% of the subjects with eGFR<60, 89.1% with eGFR 60-90 and 83.7% with eGFR>90ml/min/1.73m^2 (table 1).

Table-1: **Baseline characteristics of All Subjects**

Sr. No.	Demographic Characteristics	
1.	Mean age (±SD)	56.16 (±11.79) years
2.	Gender (Male)	65%
3.	Plasma Cystatin C	
	< 0.95 mg/L	12% (Mean ±SD 0.80±0.07)
	>0.95 mg/L	88% (Mean ± SD 1.25±0.18)
4.	eGFR	
	<60 ml/min/1.73m^2	17% (Mean ± SD 46.87±0.18)
	60-90 ml/min/1.73m^2	46% (Mean ± SD 72.82±9.37)
	>90 ml/min/1.73m^2	37% (Mean ± SD 100.08±10.15)

Our study also evidenced a significant association between Cystatin C >0.95 mg/L with diabetes and hypertension. High Cystatin C (>0.95 mg/L) was found in 47% of the total diabetic and 94.2% of the total hypertensive patients. Our study recorded a significant association between high Cystatin C (>0.95 mg/L) and smoking. Of the total smokers, 94.3% were found to have Cystatin C >0.95 mg/L. Our study evidenced a negative correlation between high Cystatin C (>0.95 mg/L) and HDL levels (table 2).

Table-2: **Relationship of Cystatin C with cardiovascular risk factors**

Level of plasma Cystatin C (mg/L)	Mean Cholesterol level (mg/dl)	Mean HDL (mg/dl)	Mean LDL (mg/dl)	Mean TG (mg/dl)	Number of Diabetics (%)	Number of Hypertensive (%)	Number of Smokers (%)
<0.95	154.83	47.75	102.67	156.50	17.5%	5.8%	5.7%
>0.95	172.77	39.07	106.28	164.05	82.5%	94.2%	80.9%
p value	0.221	0.043	0.740	0.782	0.05	0.046	0.038

DISCUSSIONS

In our study, the scatter for Plasma Cystatin C of the studied population was found to be elevated i.e, 1.19+0.22 mg/L. Mean Cystatin C level was elevated in ACS patients as compared to healthy controls (p<0.01) in studies done by P. Srilakshmi *et al*.[7], Batra *et al*.[11] and Lodh *et al*.[12] also

In our sample the cut off point for the upper limit of Cystatin C was 0.95mg/L. Study population was divided into two groups: 1)Cystatin C <0.95mg/L, 2) Cystatin C >0.95mg/L. Of the total patients, 88% had elevated Plasma Cystatin C levels of >0.95mg/L with a mean Cystatin C level of 1.25+0.18 mg/L, whereas in the study by Garcia Acuna *et al*. [13] Cystatin C levels of >0.95mg/L was found in 55% of the patients only. The study done by Batra *et al*.[11] categorized the patients into two groups (Plasma Cystatin C levels >/<1.45mg/L) ,revealed that patients with Cystatin C >1.45mg/L had 1.7 times higher relative risk of having triple vessel disease and 1.9 times higher relative risk of having diffuse CAD on coronary angiography. This could be explained by the fact that even mild renal Impairment as indicated by high plasma Cystatin C is associated with an increased cardiovascular risk.

In our study population the mean Cystatin C levels in patients with NSTEMI and STEMI was 1.22+0.21 mg/L and 1.18+0.23 mg/L respectively. In a study by Abid *et al*. [14], the mean Cystatin C levels in patients with NSTEMI and STEMI was 0.99+.028 and 1.13+0.25 respectively and it was statistically significant. Whereas, Jinjin Zhang *et al*. [15], in their study population found the mean Cystatin C levels to be 1.46+ 0.58 and 1.34+0.34 in patients with NSTEMI and STEMI respectively and these result were statistically not significant. Our study also showed Cystatin C levels were slightly higher in NSTEMI group than STEMI group but however there was no statistical significance between the two groups.

It has been known that patients with end stage renal disease have a high prevalence of cardiovascular disease and thus higher mortality rates. Mild renal impairment has also been shown to be strongly associated with cardiovascular morbidity and mortality in patients with atherosclerotic disease. Therefore measurement of renal function has become one of the risk markers for early risk stratification of the patients with ACS.

In our study population, of the 17 patients who had eGFR <60mL/min/1.73m^2, 16 patients (94.11%) had elevated Cystatin C levels i.e. >0.95mg/L (1.20+0.22) and only 1 patient had Cystatin C level <0.95 (p=0.008), which was significant. In the study by Garcia Acuna *et al*.[13], they found Cystatin C to be elevated in 54 patients whose eGFR was <60, whereas 9 patients had Cystatin C<0.95mg/L in the same group and this difference was reported to be statistically significant (p <0.001). Wolfgang *et al*.[16] included 1033 ACS patients and reported Cystatin C levels to be in the upper quintile in 70.2% of the patients with eGFR<60 (p<0.001).

In our study of the 46 patients whose eGFR was between 60-90, 41 patients had elevated Cystatin C i.e. >0.95mg/L with mean Cystatin C of 1.26+0.12 and 5 patients had Cystatin C <0.95mg/L with a mean Cystatin C of 0.86+0.03 and the p-value was highly significant (p=0.000). Garcia Acuna *et al*.[13] found that among the patients who had eGFR between 60-90, Cystatin C was >0.95mg/L in 52 patients and <0.95mg/L in 45 patients, however this difference was not statistically significant (p=0.1). Wolfgang *et al*.[16] reported Cystatin C levels to be in the upper quintile in 28.6% of the patients with eGFR 60-90.

In our study 37 patients had eGFR>90, of which 31 patients had elevated Cystatin C i.e. >0.95mg/L (1.26+0.23) and 6 had Cystatin C< 0.95mg/L (0.76+0.07) and the p-value was highly significant (p=0.000). Garcia Acuna *et al*.[13], in their study found that Cystatin C was >0.95 in 7 patients and <0.95mg/L in 36 patients, among the patients who had eGFR>90. Wolfgang *et al*.[16] reported Cystatin C levels to be in the upper quintile in 8.1% of the patients with eGFR>90.

Garcia Acuna *et al*.[13] reported that the elevated level of Cystatin C was associated with a poorer cardiovascular prognosis even in the group of patients with normal glomerular filtration. In addition, it indicates that Cystatin C is an independent predictor of cardiovascular complication in patients with coronary heart disease even in patients with normal glomerular filtration rate.

The strong association between renal function and mortality can be explained by the fact that renal dysfunction may directly contribute to atherosclerosis by causing changes in parameters like blood pressure, lipids, lipoproteins, homocysteine, and CRP. Another reason for poor prognosis could be that patients with ACS and renal dysfunction are less likely to receive adequate treatment compared to those without renal dysfunction.

In our study the mean Cystatin C level in diabetic patients was found to be 1.17+0.25. As much as 82.5% of the total diabetic patients (47/57) had Plasma Cystatin C >0.95 and the difference was statistically significant (p=0.05). In a study done on Indian population by Bablu Shukla *et al*.[10], mean plasma Cystatin C level was found to be 0.93+0.24 in CAD patients with diabetes which was higher as compared to patients without CAD and was statistically significant (p<0.001), suggesting that Plasma Cystatin C level is one of the risk factors predisposing to ACS. These results suggests a strong association between

Cystatin C and diabetes and that Cystatin C could be more than simply a marker of renal dysfunction however the mechanism responsible for this association needs to be further evaluated.

In our study 94.2% of the total hypertensive patients (49/52) were found to have Cystatin C levels of >0.95mg/L (1.24+0.23) which was statistically significant when compared to the patients who were hypertensive with Cystatin C<0.95mg/L (p=0.04). Garcia Acuna *et al*. [13] reported that, in the patient group with Cystatin C levels>0.95mg/L, 69.9% were hypertensive which was statistically significant (p= 0.001). These findings suggest that early variation in kidney function in persons without clinically recognized kidney disease might play a role in the pathogenesis of hypertension in patients with high Cystatin C values. Moreover Cystatin C is directly involved in atherosclerosis, thus explaining its predictive value in development of hypertension.

In our study 94.3% of the smokers (50/53) had elevated Cystatin C levels of >0.95mg/L and this was statistically significant (p=0.03). Garcia Acuna *et al*. [13] found that among the patients who had elevated levels of Cystatin C i.e. >0.95mg/L, 46.9% were smokers with a p-value of 0.08. In another study by Wolfgang *et al*. [16], it was reported that cigarette smoking was independently associated with high Cystatin C concentration.

The smoking related hemodynamic events may have an acute influence on renal function and therefore is a risk factor for the development and progression of kidney disease and hence increases the risk of cardiovascular morbidity and mortality. Smoking also is one of the leading risk factor for atherosclerosis which may account for high levels of Cystatin C in patients who are smokers and have ACS.

In our study, patients with Cystatin C>0.95mg/L had mean HDL level 39.07+14 mg/dl, which was lower as compared to patients with Cystatin C<0.95mg/L i.e., 47.75+10.54 thereby showing a negative correlation, the difference being statistically significant (p=0.043). This finding was similar to the study by Lodh *et al*.[12], Muntner *et al*.[17] and Parikh *et al*.[18]

The total cholesterol, mean LDL levels and triglyceride levels in our study were found to be raised in the population with Cystatin C>0.95 as compared to population with Cystatin C<0.95. However, this difference was found to be statistically insignificant in our study.

CONCLUSION

In conclusion, we found high levels of Cystatin C levels in patients with ACS. The raised levels of Cystatin C were significantly associated with eGFR, diabetes, hypertension, smoking, HDL but Total Cholesterol, LDL and Triglycerides did not show any significant association. The determination of Cystatin C at the time of hospitalization in patients with ACS may be a good clinical tool for cardiovascular risk stratification and clinical outcomes even in patients with preserved renal function

REFERENCES

1. Misra A, Nigam P, Hills AP, Chadha DS, Sharma V, Deepak KK, Vikram NK, Joshi S, Chauhan A, Khanna K, Sharma R. Consensus physical activity guidelines for Asian Indians. Diabetes technology & therapeutics. 2012 Jan 1;14(1):83-98.
2. Carda R, de Agustin JA, Manzano MC, Garcia-Rubira JC, Fernandez-Ortiz A, Vilacosta I. Valor pronostico intrahospitalario del filtrado glomerular en pacientes con sindrome coronario agudo y creatinina normal. Rev Esp Cardiol 2007;60:714-9.
3. Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furger CD. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. J Am Coll Cardiol 2001; 38:705-11.
4. Cockcroft DW, Gault MH. Prediction of cretinine clearance from serum creatinine. Nephron. 1976;16:31-41.
5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med. 1999; 130:461-70.
6. Stevens LA, Coresh J, Greene T, Levey AS. Assesing kidney function — measured and estimated glomerular filtration rate. N Engl J Med. 2006; 354:2473-83.
7. P. Srilakshmi, M. Vijaya Bhaskar, P. Prabhakara Rao, K Rambabu, M.F. Gopinath, G. Srinivasa Reddy. Prognostic Significance of Cystatin C in Coronary Artery Disease, Sch. J. App. Med. Sci., 2014;2(3C):1028-1032.
8. Shlipak MG, Katz R, Sarnak MJ, Fried LF, Newman AB, Stehman-Breen C, Seliger SL, Kestenbaum B, Psaty B, Tracy RP, Siscovick DS. Cystatin C and Prognosis for Cardiovascular and Kidney Outcomes in Elderly Persons without Chronic Kidney DiseaseCystatin C and Prognosis in Elderly Persons without Chronic Kidney Disease. Annals of internal medicine. 2006 Aug 15;145(4):237-46.
9. Silva D, Cortez-Dias N, Jorge C, Marques JS, Carrilho-Ferreira P, Magalhães A, Martins SR, Gonçalves S, da Silva PC, Fiúza M, Diogo AN. Cystatin C as prognostic biomarker in ST-segment elevation acute myocardial infarction. The American journal of cardiology. 2012 May 15;109(10):1431-8.
10. Bhat K, Lal AK, Ahmad S, Kakkar M. Cystatin C: An early marker of cardiac complications in

Diabetes. Acta Medica international 2015;2(1):84-86.

11. Batra A, Kapoor A, Sharma RK, Agrawal N, Sinha A, Kumar S, Garg N, Tewari S, Goel PK. Association of plasma cystatin C levels with angiographically documented coronary artery disease in patients of Indian origin. Journal of cardiology. 2012 Mar 31;59(2):182-9.
12. Moushumi Lodh, Ashok Parida, Joy Sanyal, Arunangshu Ganguly. Cystatin C in Acute Coronary Syndrome. The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine. 2013 Jul; 24(2): 61–67.
13. Acuña JM, González-Babarro E, Shamagian LG, Peña-Gil C, Pérez RV, López-Lago AM, Feijoó MG, González-Juanatey JR. Cystatin C provides more information than other renal function parameters for stratifying risk in patients with acute coronary syndrome. Revista Española de Cardiología (English Edition). 2009 May 1;62(5):510-9.
14. Leila Abid, Salma Charfeddine, Samir Kammoun, Mouna Turki, Fatma Ayedi. Cystatin C: A prognostic marker after myocardial infarction in patients without chronic kidney disease. J Saudi Heart Assoc 2016; 28:144–151.
15. Jinjin Zhang1, Xianhao Wu, Peizhen Gao and Pingping Yan. Correlations of serum cystatin C and glomerular filtration rate with vascular lesions and severity in acute coronary syndrome. BMC Cardiovasc Disord. 2017; 17: 47.
16. Wolfgang Koenig, Dorothee Twardella, Hermann Brenner, Dietrich Rothenbacher. Plasma Concentrations Of Cystatin C In Patients With Coronary Heart Disease And Risk For Secondary Cardiovascular Events: More Than Simply A Marker Of Glomerular Filtration Rate. Clinical Chemistry Feb 2005,51(2):321-7.
17. Muntner P, Mann D, Winston J, Bansilal S, Farkouh ME. Serum cystatin C and increased coronary heart disease prevalence in US adults without chronic kidney disease. Am J Cardiol 2008; 102:54–7?
18. Parikh NI, Hwang SJ, Yang Q, Larson MG, Guo CY, Robins SJ, Sutherland P, Benjamin EJ, Levy D, Fox CS. Clinical correlates and heritability of cystatin C (from the Framingham Offspring Study). The American journal of cardiology. 2008 Nov 1;102(9):1194-8.