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Evaluation of the Significance of Cystatin C Levels in Patients Suffering from Coronary Artery Disease

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Objectives. Cystatin C is a novel marker used in the diagnosis of preclinical chronic kidney disease (CKD). The aim of the study was to assess the role of cystatin C in the diagnosis of coronary artery disease.
Material and Methods. The study involved 63 patients of a mean age of 62.7 ± 9.5 years. The population was divided into two groups: Group I were patients with angiographically diagnosed coronary artery disease (CAD) with their first acute coronary syndrome (ACS, n = 45); Group II were patients who had clinically diagnosed coronary disease but were negative on angiography (n = 18). Cystatin C levels were measured before angiography in both groups; in Group I they were also measured 6 months after discharge.
Results. Cystatin C levels were significantly higher in Group I (p = 0.01), and this depended on the type of CAD: non-ACS, non-ST elevated myocardial infarction (NSTEMI) or ST elevated myocardial infarction (STEMI) (p = 0.01). Cystatin C levels correlated inversely with the left ventricular ejection fraction in the whole study population (p = 0.003) and in patients with NSTEMI (p = 0.03). A high cystatin C level was found to be a risk factor for ACS (OR: 1.002 95% CI [1.00029–1.004], p = 0.02) and STEMI (OR: 1.0009 95% CI [0.99–1.002], p = 0.04) but not for NSTEMI (OR: 0.99 95% CI [0.99–1.0], p = 0.21. A ROC analysis revealed that there is a significantly higher risk of ACS above a cystatin C level of 727.85 ng/mL (OR: 5.5 CI [1.65–18.3], p = 0.004) and a significantly higher risk of STEMI above 915.22 ng/mL (OR: 5.9 CI [1.7–19.7], p = 0.003).
Conclusions. The available data suggest that a high cystatin C level is a risk factor for ACS and STEMI. This could play an important role in the early diagnosis and prevention of adverse cardiovascular events (**Adv Clin Exp Med 2014, 23, 4, 551–558**).

Key words: cystatin C, coronary artery disease, STEMI, NSTEMI, acute coronary syndrome, risk factor.

Chronic kidney disease (CKD) is a growing problem in everyday clinical practice. It is said that in Poland alone it affects 4 m patients and the number is growing rapidly [1]. CKD is also a significant risk factor for cardiovascular disorders, which was described for the first time 30 years ago. It is said that a 25-year-old dialyzed patient with end-stage renal failure has the same life expectancy as a healthy eighty-year-old [2]. There have been several randomized prospective clinical trials describing the relationship between CKD and coronary artery disease (CAD), including the TRACE, SOLVE and SAVE trials. The GRACE trial, involving 12,000 patients with acute coronary syndrome (ACS), confirmed previously published data showing that even a decrease in the glomerular filtration

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rate (GFR) of as little as 30–60 mL/min doubles the risk of in-hospital death, while a severe decrease in GFR is known to be associated with a quadrupled risk of in- hospital death [3]. Analogical data has been provided by several other studies: The Kaiser Permanente Northern California Registry (1.2 m patients) linked an unequivocally decreased GFR with an increased incidence of in-hospital death, adverse cardiovascular events and a need for hospitalization. In that study, reductions in GFR of 45–59 mL/min, 30–44 mL/min, 15–29 mL/min and < 15 mL/min were associated with increases in mortality 20%, 80%, 220% and 490% respectively [4]. A multivariable analysis of the results acquired in the Valiant trial indicated that every GFR decrease of 10 mL/min (starting from just below 81 mL/min) is associated with a 10% higher risk of death or a non-fatal cardiovascular event [5].

Routine assessment of GFR by means of a calculation based on the creatinine level remains a widely used standard in clinical practice. However, it must be acknowledged that the creatinine-based GFR calculation may be burdened with considerable error. Creatinine level is dependent on many variables, such as gender, age, race, total body muscle weight, nutritional status, infection, diet or post-exercise state. Several agents such as salicylans, trimethoprim, cimetidine can also have a great impact on the serum creatinine level and therefore on the GFR calculation [6, 7]. It should be also appreciated that bilirubin level, glycemic status, uric acid concentration or furosemide and cephalosporin administration can affect the chemical reactions used in the creatinine level assay. Older age and cahexia can also result in higher GFR calculations, because the total body creatinine in these cases is lower than average. It is also known that even significant reductions in GFR are not necessarily associated with higher creatinine levels, which can peak later when GFR levels are severely reduced (< 50%). In clinical practice this situation may lead to a misdiagnosis of renal failure. In light of such problems, new and more sensitive markers of renal failure are sought.

In recent years major scientific efforts concerning early detection of renal failure have been focused on a protein called cystatin C. First described in 1985, cystatin C has proved useful in the diagnosis of the early stages of chronic kidney disease, even pre-clinical stages [8, 9]. A study by Mussap et al. showed that a decrease in GFR from 120 mL/min/1.73 m^2 to 20 mL/min/1.73 m^2 has a much stronger correlation with an elevation of cystatin C then with an elevation in creatinine levels ($p < 0.05$) [10].

Cystatin C is a protein produced in every eukaryotic cell. Its function consists in the inhibition of proteases such as catepsins, which are essential in the transformation and presentation of antigens, neoplastic processes and inflammation. It is said that cystatin C is an immunologic system modulator, as it impacts the transformation of MHC II complexes, stimulates NO synthesis in macrophages, and the synthesis of TNF and interleukin-10 as well. Cystatin C is produced and secreted by cardiomyocytes, and its synthesis is elevated when the heart is subjected to ischemia. The effector molecules of cystatin C have not yet been well described [11]. Normally, cystatin C is filtered by the renal glomeruli and catabolized by renal tubular cells. Its accumulation can lead to adverse effects, such as a build-up of amyloid deposits in vascular walls. Cystatin C appears not only to be a useful marker for renal disease but may also carry additional valid information of cardiovascular risk in patients with coronary artery disease.

Material and Methods

The study involved 63 patients (26 women and 37 men) hospitalized in the Department and Clinic of Cardiology at Wroclaw Medical University in Wroclaw, Poland, between 2009 and 2010. The mean age of the study population was 62.7 ± 9.5 years. The patients were divided into 2 groups: Group I included patients with coronary artery disease, undergoing their first acute coronary syndrome (ACS) diagnosed by coronary angiography (n = 45: 15 women, 30 men); Group II were patients who had clinically diagnosed coronary disease, based on high probability of CAD or a positive or non-diagnostic ECG cardiac stress test, but whose coronary angiographies gave negative results (n = 18; 11 women, 7 men). The patients with ACS were treated according to European Society of Cardiology guidelines for ACS, while the patients without ACS were treated in accordance with treatment standards for their conditions. Written informed consent was obtained from all patients taking part in the study. The study was approved by the Local Ethics Committee (No. KB–543/2008).

Cystatin C levels were measured with the use of commercially available Cystatin C Human Elisa Kits (Biovendor Inc.). The samples needed for the assessment of cystatin C were collected in both groups shortly before the coronary angiography, and in Group I samples were also collected 6 months after discharge. Transthoracic echocardiograms (TTE) were carried out using a Vivid 4 ultrasound (GE). The left ventricular ejection fraction (LVEF) was measured by Simpson's method in 2D projections.

The collected data were analyzed using Statistica 9 software. The normality of the distribution was assessed by the Shapiro-Wilk test. When normally distributed, the data were compared using Student's *t*-test, the ANOVA *F*-test for independent variables and Pearson's correlation coefficient. When not normally distributed, the data were analyzed with Mann-Whitney's test, the nonparametric ANOVA *F*-test and calculation of Spearman's correlation coefficient. Additional analyses of logistic regression and receiver-operator curves (ROC) were conducted where appropriate. Statistical significance was assumed at $p < 0.05$.

Results

Neither group different in terms of age and gender. The prevalence of arterial hypertension, diabetes, heart failure and atrial fibrillation was equal in the two groups. Neither group showed any statistical differences in the advancement of CKD, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) staging of CKD. The patients in Group I (ACS) showed a lower prevalence of nicotine abuse ($p = 0.04$), a higher white blood count ($p = 0.001$) and a lower LVEF ($p = 0.001$) than the patients in Group II (non-ACS). The estimated GFR (eGFR) did not differ between the two groups, although the cystatin C level was significantly higher in Group I ($p = 0.01$, Table 1). It was found that cystatin C level was significantly dependent on the type of CAD (non-ACS, ACS:NSTEMI or ACS:STEMI; $p = 0.01$). Post-hoc analysis revealed that cystatin C levels were significantly higher in patients with the diagnosis of ACS:STEMI in comparison with patients without ACS ($p = 0.02$). The eGFR values in the same analysis did not depend on the type of CAD ($p = 0.88$). Table 2 presents a correlation matrix for cystatin C level and the remaining variables.

In the present study, the cystatin C level correlated inversely with the LVEF in all the patients ($p = 0.003$). An analogical correlation was observed between the eGFR and the LVEF, although it did not reach statistical significance ($p = 0.18$). With age, cystatin C level appeared to elevate without statistical significance ($p = 0.18$), and the eGFR appeared to decline significantly ($p = 0.001$).

The inverse correlation between cystatin C level and LVEF was also found within the STEMI and NSTEMI subgroups of ACS, as shown in Table 3. In patients with ACS: STEMI, there was a trend towards lower LVEF with an increase in cystatin C level ($p = 0.18$). In patients with NSTEMI the same relationship was statistically significant ($p = 0.03$).

An ROC analysis was conducted in order to determine the cut-off point for cystatin C above which there is a significantly higher risk of ACS in patients with CAD. The results are shown in Fig. 1–3. As shown in Fig. 1, the point above which there was a significantly higher risk of ACS was found at 727.85 ng/mL (sensitivity: 82.6%, specificity: 40.3%). A univariate analysis showed that a cystatin C level of 727.85 ng/mL increases the risk of ACS fivefold (OR: 5.5 [95% CI 1.65–18.3]; $p = 0.004$) Interestingly, 73.3% of patients in Group I (ACS) had a cystatin C level higher than the cut-off point of 727.85 ng/mL, as opposed to Group II (non-ACS), where only 38.9% of patients had higher levels ($p = 0.02$). In a multivariate analysis involving such variables as gender, age, diabetes mellitus, arterial hypertension, CKD, nicotine abuse and obesity, this cystatin C cut-off point was an even stronger risk factor for ACS (OR : 8.28 [95% CI 1.62–42.2]; $p = 0.001$). A similar analysis carried out for eGFR did not find any significant cut-off points above which the risk of ACS was higher. It is noteworthy that both in the ACS group and in the whole study population, the mean eGFR results were similar in patients who had cystatin C levels both below and above the cut-off point of 727.85 ng/ /mL ($p = 0.94$ and $p = 0.4$ respectively).

An ROC analysis was also conducted in order to find the cut-off point above which the risk of ACS:STEMI was significantly higher. This was found at 915.22ng/mL (sensitivity: 81.8%, specificity: 37.5%). A similar value for the eGFR could not be described. In the univariate analysis, a cystatin C level of 915.22 ng/mL increased the risk of STEMI nearly sixfold (OR: 5.9 [95% CI 1.7–19.7]; $p = 0.003$). A multivariate analysis based on such variables as gender, age, diabetes mellitus, arterial hypertension, CKD, nicotine abuse and obesity described the cystatin C level cut-off point of as a stronger risk factor for ACS:STEMI (OR: 6.21 [95% CI 1.7–22.4]; $p = 0.004$). As many as 77.3% of the ACS:STEMI patients had levels of cystatin C higher than the cut-off point of 915.22 ng/mL, as opposed to patients without ACS:STEMI, in whom only 36.6% had levels higher than the cut-off point ($p = 0.001$). In patients with ACS:STEMI, mean eGFR levels were similarfor patients with higher and lower cystatin C levels than the cut-off point ($p = 0.94$). A similar observation could be made for the whole study population ($p = 0.47$).

Another analysis was carried out to identify the cut-off point above which patients experienced a significantly higher risk of ACS:NSTEMI: 1336.95 ng/mL, although it was associated with low sensitivity and specificity (33.3% and 8.5% respectively), which means it cannot be treated as a marker for NSTEMI in patients with CAD.

Table 1. Characteristics of the study population

Data	Group I (n = 45)	Group II (n = 18)	p
Demographic data			
Gender	w: 15 (33.3%) m: 30 (66.7%)	w: 11 (61.1%) m: 7 (38.9%)	0.08
Age	64.1 ± 9.3	60.0 ± 9.7	0.14
Admission day data			
STEMI	22 (48.9%)	0 (0%)	0.001
NSTEMI	23 (51.1%)	0 (0%)	0.001
Obesity	3 (6.7%)	3 (16.7%)	0.46
Nicotine abuse	4 (8.9%)	6 (33.3%)	0.04
Arterial hypertension	30 (66.7%)	12 (66.7%)	0.77
Arterial hypertension stage I	8 (17.8%)	6 (33.3%)	0.31
Arterial hypertension stage II	17 (37.8%)	6 (33.3%)	0.97
Arterial hypertension stage III Atrial fibrillation	5 (11.1%) 7 (15.6%)	0 (0%) 2 (11.1%)	0.34 0.95
Heart failure	2 (4.4%)	0 (0%)	0.91
Diabetes type 2 CKD CKD I° CKD II° CKD III° CKD IV° CKD V°	8 (17.8%) 40 (88.9%) 2 (4.4%) 21 (46.7%) 8 (17.8%) 6 (13.3%) 8 (17.8%)	2 (11.1%) 15 (83.3%) 0 (0%) 11 (61.1%) 4 (22.2%) 3 (16.7%) 0 (0%)	0.79 0.86 0.91 0.45 0.96 0.95 0.13
Laboratory data			
LDL [mg/dL]	142.4 ± 48.2	139.2 ± 39.1	0.82
HDL [mg/dL]	42.4 ± 11.3	53.1 ± 12.3	0.08
Total cholesterol [mg/dL]	215.4 ± 51.6	223.6 ± 43.8	0.57
Trigliceride [mg/dL]	135.4 ± 82.3	146.2 ± 50.2	0.31
Creatinine [mg/dL]	1.4 ± 0.91	1.35 ± 0.77	0.27
eGFR [mL/min/1.73 m^2]	74.0 ± 21.9	73.7 ± 19.3	0.95
Cystatin C [ng/mL]	1182.6 ± 1000.7	763.5 ± 282.8	0.01
WBC [10^3/uL]	10.6 ± 3.6	7.4 ± 1.9	0.001
Other data			
LVEF [%]	54.9 ± 1.2	66.8 ± 8.1	0.001

Logistic regression (univariate model) once more confirmed that cystatin C is a risk factor for ACS (OR:1.002 95% CI (1.00029–1.004); p = 0.02), as opposed to eGFR (OR: 1.002 95% CI (0.97–1.03); p = 0.87). In this analysis cystatin C level was again a risk factor for ACS:STEMI (OR: 1.0009 95% CI (0.99–1.002); p = 0.04) but not for ACS:NSTEMI (OR: 0.99 95% CI (0.99–1.0); p = 0.21). eGFR did not reach statistical significance as a risk factor in the study population (OR: 0.99 95% CI (0.97––1.02); p = 0.92).

Finally, the analysis indicated that in the 6-month follow-up, a steady elevation in cystatin C level was observed in the patients in Group I

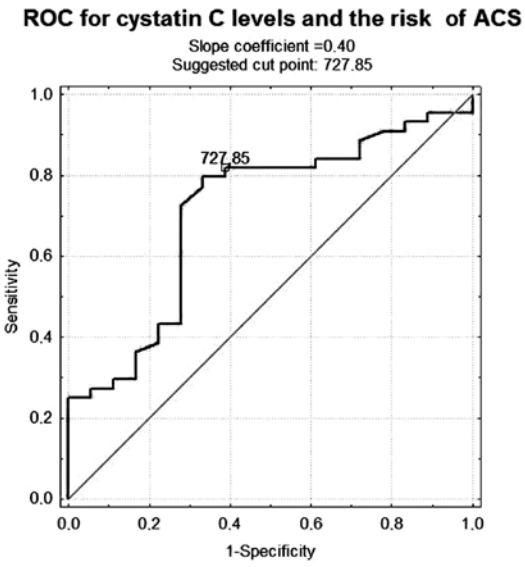

Fig. 1. ROC for cystatin C levels and the risk of ACS

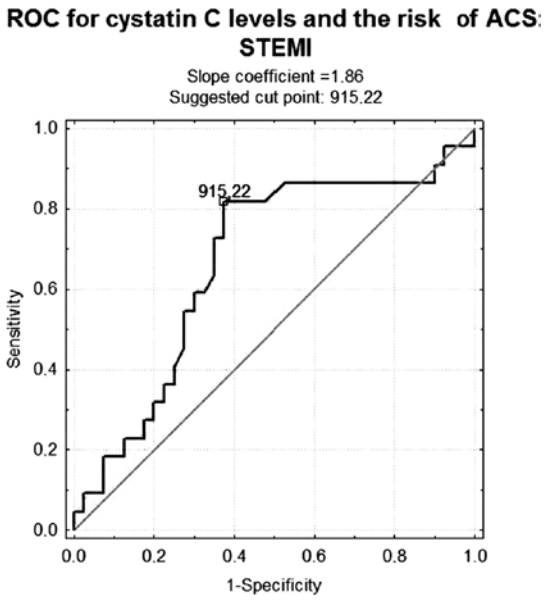

Fig. 2. ROC for cystatin C levels and the risk of ACS – STEMI

(p = 0.04). In the subgroup analysis (ACS:STEMI vs. ACS:NSTEMI), no intergroup differences were observed in terms of the 6-month cystatin C level elevation.

Discussion

Chronic kidney disease is a significant burden for patients suffering from coronary artery disease. In patients with CAD, CKD elevates the risk of major adverse cardiovascular events and death. Monitoring renal function is an element of

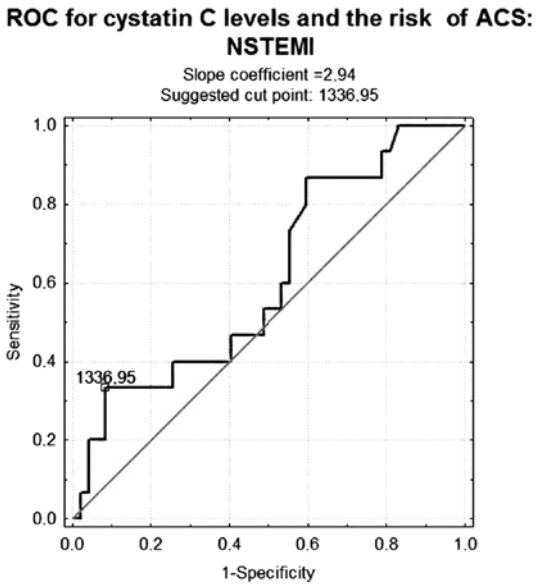

Fig. 3. ROC for cystatin C levels and the risk of ACS – NSTEMI

everyday care of patients hospitalized in the cardiology ward. Many recent studies of cystatin C in renal failure indicate that this protein is a useful marker for the diagnosis of the preclinical stages of CKD even when creatinine levels and eGFR are still within the normal values. This is of the utmost importance for patients in whom potentially nephrotoxic agents, such as ACE inhibitors, are used for cardiovascular therapy. It allows for modifications of therapy at early stages of renal injury in patients at a high risk of renal failure. The aim of the present study was to evaluate the relationship between the cystatin C levels and coronary artery disease. The analyses showed that cystatin C levels have a tendency to increase with age (p = 0.15); similar observations were made by Finney and Flisser. [12, 13]. Moreover, cystatin C levels are significantly correlated with the systolic function of the left ventricle. This observation is supported by the fact that the migration of macrophages to vulnerable plaque can be regulated by cystatin C secreted from cardiomyocytes. In contast to cystatin C, eGFR did not correlate with LV systolic function in the same analysis; eGFR presented only as a non-significant trend (p = 0.18). The most important finding of the current study is the fact that elevated cystatin C levels increase the risk of ACS and ACS: STEMI in patients with coronary artery disease. Cystatin C levels of 727.85 mg/mL and above significantly increased the risk of ACS (more than 5 times), and when levels rose to more than 915.22 ng/mL the risk of ACS: STEMI increased almost 6 times. It is worth mentioning that an analogical cut-off point for eGFR and the risk of ACS

Table 2. Correlation matrices for cystatin C and eGFR with the continuous variables studied

Correlation matrix – Cystatin C						
	Total no. of patients (n = 63)		**Group I (n = 45)**		**Group II (n = 18)**	
	R – Spearman	**p**	**R – Spearman**	**p**	**R – Spearman**	**p**
Cystatin C & age	0.20	0.15	0.13	0.43	0.23	0.36
Cystatin C & WBC	0.14	0.30	–0.15	0.39	0.05	0.84
Cystatin C & LVEF	–0.39	0.003	–0.13	0.43	–0.42	0.08
Cystatin C & Tot Chol	–0.05	0.70	–0.07	0.69	0.07	0.8
Cystatin C & LDL	0.005	0.97	–0.03	0.88	–0.03	0.92
Cystatin C & HDL	0.045	0.74	0.18	0.28	0.04	0.88
Cystatin C & TG	–0.17	0.24	–0.13	0.43	0.006	0.98
Cystatin C & GFR	–0.12	0.39	–0.14	0.41	–0.14	0.57
Correlation matrix – eGFR						
	Total no. of patients (n = 63)		**Group I (n = 45)**		**Group II (n = 18)**	
	R – Spearman	**p**	**R – Spearman**	**p**	**R – Spearman**	**p**
eGFR c & age	–0.44	0.001	–0.37	0.03	–0.62	0.01
eGFR c & WBC	–0.11	0.43	–0.10	0.54	–0.09	0.73
eGFR c & LVEF	–0.18	0.18	–0.09	0.60	–0.42	0.08
eGFR c & Tot Chol	0.03	0.84	–0.03	0.86	0.19	0.47
eGFR c & LDL	0.05	0.74	0.00	0.98	0.14	0.58
eGFR c & HDL	–0.14	0.32	–0.17	0.32	–0.09	0.73
eGFR c & TG	0.04	0.78	0.05	0.77	0.08	0.75

could not be calculated, which does not mean that decreased eGFR is not a risk factor for adverse cardiovascular events in patients with CAD. Another fact that should be acknowledged is that the mean eGFR values in the ACS group, the ACS:STEMI subgroup and in the whole study population did not differ among patients with cystatin C levels lower or higher than the cut-off points. This suggests that eGFR is not best suited for the assessment of cardiovascular risk in patients with chronic kidney disease. In light of this evidence, it may be concluded that measuring cystatin C levels in the CAD population may provide more information on LV systolic function and ACS/ACS: STEMI risk than measuring eGFR alone. Patients surviving ACS, ACS:NSTEMI or ACS:STEMI, despite sufficient therapy, experienced further elevation of the cystatin C levels. In view of the available data, it seems that observing cystatin C concentration after percutaneous coronary angioplasty may provide some new prognostic information on the patients. Zhao et al. found that a higher level of cystatin C is an independent risk factor for restenosis in stents in patients with ACS [14].

This study suggests that cystatin C level could be a significant negative predictor of acute coronary syndromes. Moreover, it correlates more strongly with left ventricular systolic injury than eGFR does. Assessing cystatin C levels in patients suffering from acute coronary syndrome may provide more information on individual cardiovascular risk than is provided by eGFR, especially in those cases when eGFR remains within the normal range.

Limitation of Study

The main limitation of this study is the small number of patients who were included.

Table 3. Correlation matrices for cystatin C and eGFR with the continuous variables studied – subgroup analysis of patients suffering from STEMI and NSTEMI

Correlation matrix – Cystatin C				
	STEMI (n = 22)		**NSTEMI (n = 23)**	
	R – Spearman	**p**	**R – Spearman**	**p**
Cystatin C & age	0.16	0.48	0.20	0.48
Cystatin C & WBC	–0.17	0.46	–0.27	0.35
Cystatin C & LVEF	–0.27	0.18	–0.55	0.03
Cystatin C & Tot Chol	–0.05	0.84	–0.18	0.52
Cystatin C & LDL	–0.07	0.76	–0.09	0.74
Cystatin C & HDL	0.26	0.26	0.15	0.59
Cystatin C & TG	–0.07	0.75	–0.34	0.22
Cystatin C & GFR	–0.14	0.54	–0.15	0.62
Correlation matrix – eGFR				
	STEMI (n = 22)		**NSTEMI (n = 23)**	
	R – Spearman	**p**	**R – Spearman**	**p**
eGFR c & age	–0.37	0.09	–0.33	0.25
eGFR c & WBC	–0.04	0.87	–0.10	0.71
eGFR c & LVEF	–0.04	0.84	–0.12	0.67
eGFR c & Tot Chol	0.11	0.64	–0.11	0.71
eGFR c & LDL	0.07	0.76	–0.07	0.81
eGFR c & HDL	–0.21	0.37	–0.43	0.11
eGFR c & TG	0.07	0.76	–0.02	0.94

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