Relationship Between Syntax Score and Cystatin C in Patients with Acute Coronary Syndrome

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ABSTRACT

Introduction: The SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score (SS) is an angiographic scoring system to determine the severity of coronary artery disease (CAD). As far as we know, studies examining the relationship between SYNTAX Score and Cystatin C (Cys-C) are limited in the literature. In this study, we aimed to investigate the relationship between Cys-C level and SS in patients presenting with ST-elevation myocardial infarction (STEMI).

Patients and Methods: One hundred ninety-two patients who underwent coronary angiography for STEMI between June 2021 and December 2021 in our center were included in the study. The patients were divided into two groups according to their SS values: Group 1 included patients with SS< 22, and Group 2 included patients with SS≥ 22. The two groups were compared in terms of baseline characteristics and serum Cys-C levels.

Results: Patients in Group 2 had significantly higher Cys-C levels than those in Group 1 (1.7 ± 0.53 vs 1.3 ± 0.29; p= 0.006). In the correlation analysis, SS showed a positive correlation with the Cys-C level (r= 0.189, p= 0.015). Multivariate logistic regression analysis showed that Cys-C level was an independent predictor of high SS (β= 0.306, p= 0.006). When receiver operating characteristic (ROC) curve analysis was performed, the optimal cut-off value of Cys-C to predict severe coronary artery disease (indicating high SS) was Cys-C≥ 1.56, which was predictive for severe coronary artery disease with 74% sensitivity and 72% specificity [area under the curve (AUC)= 0.745, 95% confidence interval (CI)= 0.624-0.835, p< 0.001).

Conclusion: Cystatin C levels are independently associated with high SS in STEMI patients. In summary, our findings show that Cys-C is a promising clinical biomarker that can be used to assess the severity of coronary artery lesions, potentially providing additional information to established risk markers.

Key Words: Syntax score; cystatin C; ST-elevation myocardial infarction

Akut Koroner Sendromlu Hastalarda Sistatin C ile Syntax Skoru Arasındaki İlişki

ÖZET

Giriş: SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) skoru (SS), koroner arter hastalığının (KAH) şiddetini belirlemek için kullanılan bir anjiyografik skorlama sistemidir. Bildiğimiz kadarıyla literatürde SYNTAX skoru ile Sistatin C (Cys-C) arasındaki ilişkiyi inceleyen çalışmalar sınırlıdır. Bu çalışmada ST yükselmeli miyokard enfarktüsü (STEMI) ile başvuran hastalarda Cys-C düzeyi ile SS arasındaki ilişkiyi araştırmayı amaçladık.

Hastalar ve Yöntem: Çalışmaya merkezimizde Haziran 2021 ile Aralık 2021 tarihleri arasında STEMI nedeniyle koroner anjiografi yapılan 192 hasta dahil edildi. Hastalar SS değerlerine göre iki gruba ayrıldı: Grup 1 SS< 22 olan hastalar, Grup 2 SS≥ 22 olan hastalar olarak tanımlandı. Başlangıç özellikleri ve serum Cys-C düzeyleri açısından iki grup karşılaştırıldı.

Bulgular: Grup 1 ile karşılaştırıldığında, Grup 2'deki hastalarda Cys-C düzeyleri anlamlı olarak daha yüksekti (1.7 ± 0.53'e karşılık 1.3 ± 0.29; p= 0.006). Korelasyon analizinde SS, Cys-C düzeyi ile pozitif korelasyon gösterdi (r= 0.189, p= 0.015). Çok değişkenli lojistik regresyon analizi, Cys-C seviyesinin yüksek SS'nin bağımsız bir öngörücüsü olduğunu gösterdi (β= 0.310, p= 0.006). Alıcı işletim karakteristiği (ROC) eğrisi analizi yapıldığında, ciddi koroner arter hastalığını (yüksek SS) öngörmek için Cys-C'nin optimal cut-off değeri, Cys-C≥ 1.56 değerinde bulundu; ciddi koroner arter hastalığı için %74 duyarlılık ve %72 özgüllük ile öngördürücüydü [eğrinin altındaki alan (EAA)= 0.745, %95 güven aralığı (GA)= 0.624-0.835, p< 0.001).

Sonuç: Sistatin C düzeyi STEMI hastalarında bağımsız olarak yüksek SS ile güçlü bir şekilde ilişkilidir. Özetle, sonuçlarımız Cys-C'nin koroner arter hastalığının şiddetini değerlendirmek için kullanılabilecek umut verici bir klinik biyobelirteç olduğunu ve bu durumun yerleşik risk belirleyicileri için tamamlayıcı bilgiler sağlayabileceğini gösterdi.

Anahtar Kelimeler: Syntax skoru; Sistatin C; ST yükselmeli miyokard enfarktüsü

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INTRODUCTION

Coronary artery disease (CAD), a major cause of morbidity and mortality worldwide, remains one of the most pressing public health issues among cardiovascular diseases[1]. Cystatin C or Cystatin 3 (formerly gamma trace, post-gamma-globulin, or neuroendocrine basic polypeptide), a protein encoded by the CST3 gene, is mainly used as a biomarker of kidney function[2]. Epidemiological studies show that high circulating Cys-C is associated with a risk of cardiovascular disease (CVD), independent of creatinine-based renal function[3,4].

With the advancement of technology, intravascular ultrasound (IVUS) has become another accurate tool for assessing atherosclerotic burden[5,6]. The limitations of IVUS are cost and availability, as most CAD registries continue to use angiography to assess atherosclerosis severity. SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score (SS) is used as an angiographic scoring system to evaluate the severity and extent of CAD[7]. Coronary angiography has potential consequences such as radiocontrast nephropathy, vascular rupture, and hematoma, and it is not cost-effective to perform on every patient. This emphasizes the importance of non-invasive detectors (such as biomarkers) in predicting the risk and burden of CAD and taking appropriate protective measures. Although studies suggest that Cys-C may be a promising marker in this regard, the data in the literature are insufficient. Therefore, in this study, we tried to reveal the relationship of Cys-C with atherosclerotic extensivity and severity, as verified by the SYNTAX score.

PATIENTS and METHODS

Trial Design and Study Population

The study had a single center and a cross-sectional design. A total of 192 patients who underwent coronary angiography for STEMI between June 2021 and December 2021 in our center were included. Patients were divided into two groups according to their SS: Group 1 (SS< 22, mild CAD) and Group 2 (SS≥ 22, severe CAD). Patients with known CAD, severe heart valve disease, heart failure, malignancy, acute infection, severe liver disease, and renal failure and patients without written consent were excluded from the study. Type 2 diabetes mellitus was defined as a fasting blood glucose level of ≥126 mg/dL and/or previous diagnosis and treatment of diabetes [8]. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or using antihypertensive therapy and/or having known hypertension[9]. STEMI diagnosis and treatment were made according to current guidelines[10].

The study was approved by the ethics committee of XXX Faculty of Medicine and was performed in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all patients.

Biochemical Analysis

After the patients were admitted for coronary angiography, venous blood samples were taken into biochemistry tubes to study the serum Cys-C levels before the procedure. Samples were centrifuged at 4000 rpm for 15 minutes and serum were stored at -80°C until the day of analysis. Then, the Cys-C levels of all participants were studied simultaneously using the same serum samples. The enzyme-linked immunosorbent assay (ELISA) was used to measure serum Cys-C.

Coronary angiography

The Judkins technique was used to perform coronary angiography via the radial or femoral route. Two independent cardiologists reviewed all angiographic images. The SYNTAX score was calculated as follows: According to the American Heart Association (AHA) classification, the coronary tree was divided into 16 segments. Scores assigned to each lesion identified in the coronary tree with >50% diameter narrowing in vessels >1.5 mm in diameter were added. Each segment was given 1 or 2 points according to the presence of the disease. This score was then weighted according to values ranging from 3.5 for the proximal left anterior descending artery (LAD) to 5.0 for the left main and 0.5 for the smaller branches [11].

Statistical Analysis

Statistical Program for Social Sciences 20 (IBM SPSS, Chicago, IL, USA) was used for all statistical calculations. The Kolmogorov-Smirnov test was used to test the normal distribution of the data. Continuous variables were expressed as mean ± SD or median (interquartile range) and compared with Student's t or Mann-Whitney U tests according to distribution. Categorical variables were expressed as percentages and numbers, and compared with the Chi-square test. Spearman's correlation analysis was performed to determine the correlation of SS with other continuous variables. In addition, multivariate logistic regression analysis was performed to identify independent predictors of high SS. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimum cut-off value of the Cys-C level for predicting a high SYNTAX score. The statistical significance level was accepted as $p< 0.05$.

RESULTS

A total of 192 patients were included in the study. The demographic and clinical characteristics of the patients are given

Table 1. Demographic and characteristic features of patients

Variables	Group 1 n= 116	Group 2 n= 74	p
Age	54 ± 12	61 ± 13	0.028
Gender, male (%)	81 (69.8)	51 (68.9)	0.542
Diabetes mellitus, (%)	22 (18.9)	18 (24.3)	0.125
Hypertension, (%)	38 (32.7)	41 (55.4)	0.020
Hyperlipidemia, (%)	28 (24.1)	19 (25.6)	0.610
Smoking, (%)	48 (41.3)	38 (51.3)	0.029
SBP, mmHg	111 ± 11	112 ± 17	0.850
DBP, mmHg	71 ± 10	68 ± 12	0.290
Hemoglobin, (mg/dL)	14.2 ± 1.73	13.8 ± 1.42	0.390
Albumin, (mg/dL)	4.33 (4.00-4.50)	4.28 (3.90-4.40)	0.960
Uric acid, (mg/dL)	5.20 (4.20-6.10)	5.10 (4.10-6.00)	0.186
Pulse, (beats/min)	74 ± 13	75 ± 16	0.530
WBC, (10^9/L)	13.3 ± 4.2	12.5 ± 3.6	0.103
PLT, x$10^3/\mu$L	255 ± 74	242 ± 81	0.211
Hematocrit, (%)	41.8 ± 4.5	42.0 ± 4.6	0.152
CRP, mg/dL	0.53 (0.20-1.19)	0.56 (0.21-1.25)	0.253
Sediment, (mm/h)	19.0 ± 14.4	23.2 ± 22.2	0.08
BUN, (mg/dL)	15.7 ± 4.2	16.4 ± 7.1	0.324
Creatinine, (mg/dL)	0.85 ± 0.25	0.80 ± 0.25	0.06
LDL-C, (mg/dL)	105.0 (81.0-130.0)	108.0 (86.0-137.0)	0.135
HDL-C, (mg/dL)	33.0 (30.0-39.0)	33.0 (27.0-38.0)	0.580
Total cholesterol, (mg/dL)	178 (144.0-205.0)	180.0 (153.0-193.0)	0.090
Triglyceride, (mg/dL)	142.0 (101.0-211.0.)	145 (106.0-214.0)	0.107
LVEF, (%)	55 ± 9.5	53 ± 9.0	0.560
Cystatin C, (mg/L)	1.3 ± 0.29	1.7 ± 0.53	0.006

Group 1 (Syntax score< 22, mild coronary artery disease); Group 2 (Syntax score≥ 22, severe coronary artery disease).
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WBC: White blood cell count, PLT: Platelet count, BUN: Blood urea nitrogen, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction.

in Table 1. There was no significant difference between the two groups in terms of baseline demographic characteristics. However, Cys-C levels in Group 2 were significantly higher than in Group 1 (p= 0.006). In the correlation analysis, there was a positive correlation between the SYNTAX score and Cystatin C (r= 0.189, p= 0.015) (Table 2). Multivariate logistic regression analysis was performed to identify independent predictors of high SS. Cys-C and smoking were found to independently predict high SS in multivariate logistic regression analysis (β= 0.310, t= 2.759, p= 0.006; β= 0.230, t= 2.019, p= 0.045; respectively) (Table 3). The best cut-off value of Cystatin C in predicting high SS was determined by receiver operating characteristic (ROC) analysis (Figure 1). When ROC curve analysis was performed, the optimal cut-off value of Cys-C to predict severe CAD (indicating high SS) was ≥1.56; which was predictive for severe CAD with 74% sensitivity and 72% specificity [area under the curve (AUC)= 0.745, 95% confidence interval (CI)= 0.624-0.835, p< 0.001].

DISCUSSION

In this study, the aim was to examine the relationship between Cys-C and the presence of severe CAD. The main finding of our study was that serum Cys-C levels were independently associated with high SYNTAX scores, which indicate

Table 2. Correlation analysis between SYNTAX score, cystatin C, and other parameters

Variables	Correlation coefficient (r)	p
Age	0.106	0.012
SBP, (mmHg)	-0.012	0.912
e-GFR, (mL/min)	-0.001	0.979
Uric acid, (mg/dL)	0.049	0.246
Albumin, (mg/dL)	-0.178	0.128
WBC, (x1000/mm^3)	-0.046	0.379
Hematocrit, (mg/dL)	-0.135	0.158
CRP, (mg/dL)	0.093	0.029
LVEF, (%)	-0.194	0.241
LDL-C, (mg/dL)	-0.054	0.642
Creatinine, (mg/dL)	0.205	0.059
Cystatin C, (mg/dL)	0.189	0.015

CRP: C-reactive protein, LVEF: Left ventricular ejection fraction, eGFR: Estimated glomerular filtration rate, LDL-C: Low-density lipoprotein cholesterol, SBP: Systolic blood pressure, WBC: White blood cell.

Table 3. Multivariate linear regression analysis showing independent predictor of high SYNTAX score

	Unstandardized coefficients		Standardized coefficients		
Variables	B	SE	β	t	p
Hyperlipidemia	0.163	2.783	0.007	0.058	0.920
Systolic blood pressure	0.008	0.071	0.008	0.063	0.823
Hypertension	0.384	2.521	0.024	0.153	0.893
Diabetes mellitus	0.442	2.703	0.019	0.149	0.728
Age	0.101	0.092	0.151	1.128	0.213
Cystatin C	7.654	2.303	0.310	2.759	0.006
Smoking	4.541	2.253	0.230	2.019	0.045

severe CAD in STEMI patients. The findings of our study suggest that there may be a possible relationship between Cys-C level and the severity of CAD. The higher the levels of Cys-C, the higher the SYNTAX score, indicating greater severity of atherosclerotic burden in the coronary arteries. Our findings suggest that the serum level of Cys-C could be a promising biomarker for detecting the extent and severity of atherosclerotic vessel disease.

Coronary angiography is used as the gold standard diagnostic method in determining the severity of CAD[12]. For this reason, some scoring systems based on angiographic imaging have been developed. SS is a scoring system used angiographically to determine the severity and extent of CAD. The number, location, and functional significance of the lesions are all evaluated in this scoring system[12,13]. Studies have shown a relationship between high SS and adverse cardiac events[14]. Therefore, this scoring system is accepted as an independent prognostic marker widely used in CAD patients.

Atherosclerosis is a complex disease of the arteries characterized by endothelial dysfunction, vascular inflammation, and subintimal lipid deposition. Although the underlying mechanisms are controversial, many cardiometabolic risk factors facilitate the development of atherosclerosis. As the disease progresses, the formation of an atherosclerotic plaque causes the development of acute coronary syndrome, which results in platelet activation and thrombus formation after plaque erosion or rupture[15]. Previous studies have found a strong link between high Cys-C serum levels and stable CAD, acute coronary syndrome (ACS), non-ST-elevation acute coronary syndrome (NSTEMI), and ST-elevated myocardial infarction

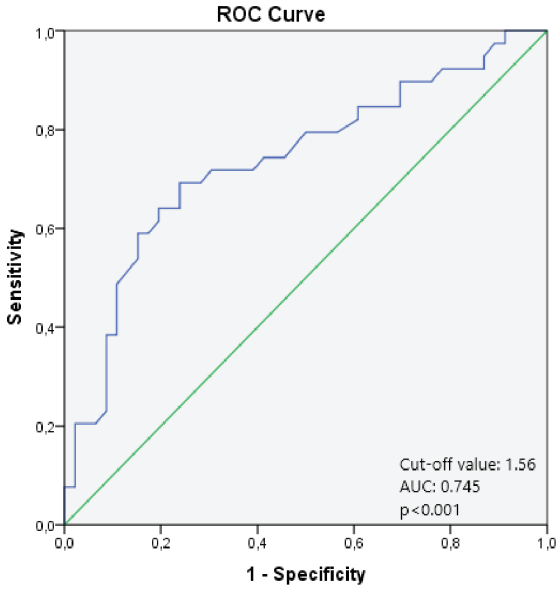

Figure 1. ROC curve analysis of Cystatin C predicting high SYNTAX score.
AUC: Area under the curve.

(STEMI)[16-20]. When the relationships between Cys-C and CAD severity were evaluated, we found a positive correlation between Cys-C serum levels and SYNTAX score. The results of our study are consistent with some past studies proving that elevated Cys-C levels are associated with the severity of CAD[18-20].

Several previous studies have demonstrated a link between SYNTAX score and CAD prognosis, such as mortality and disease progression[14,21,22]. However, few studies have highlighted the role of Cys-C in predicting the severity of atherosclerotic vessel prevalence[19,20]. The association of high Cys-C with mortality and morbidity has also been demonstrated in several cohort studies[23-27]. Furthermore, previous research has shown an independent relationship between Cys-C and the number of narrowed vessels[28]. These observations confirmed that Cys-C levels may not be merely an indicator of renal dysfunction and thus may represent more than just a marker of renal function. Thus, Cys-C may be a more potent biomarker for predicting the severity and adverse outcomes of CAD.

Cystatin C is expressed in nucleated cells, regulates the activity of cysteine protease, and plays a role in the dynamic balance of production and degradation of the extracellular matrix (ECM). Cys-C and its fragments can also affect the phagocytic and chemotactic ability of neutrophils, participate in the inflammatory process and modulate inflammatory responses[29]. Inflammation plays an important role in the development of atherosclerosis[30,31]. Several studies have shown that an imbalance in cysteine protease and its inhibitor leads to the degradation of the extracellular matrix and the development of atherosclerosis by directing monocytes, macrophages, and vascular smooth muscle cells to the intima[32,33]. Cysteine proteinase, the major enzyme in ECM degradation, and its inhibitor as Cys-C is expressed in the plaque. An excess of cysteine proteinase over Cys-C may contribute significantly to ECM destruction rendering the plaque more prone to rupture. ECM disruption and positive arterial remodeling are closely associated with plaque destabilization, suggesting that cysteine proteinase-Cys-C imbalance may facilitate plaque sensitivity as a result of ACS[34]. Several studies found that in patients with NSTE-ACS and increased cardiac troponin T concentrations, high plasma Cys-C concentrations are associated with a higher risk of death and spontaneous MI and there is evidence that both elastolytic cysteine proteases and their inhibitors, such as Cys-C, are involved in the pathogenesis of atherosclerosis[35,36]. Therefore, protease-antiprotease imbalance may be the main factor underlying the close relationship between Cys-C and acute coronary syndrome. As we found in our study, the high Cys-C levels in patients with high SYNTAX scores can be explained by the fact that as the atherosclerotic load increases, the protease-antiprotease balance in the atherosclerotic plaque deteriorates and the protective mechanisms are upregulated at that rate in the acute period. A previous experimental study showed that the absence of the protease inhibitor Cys-C in inflammatory cells resulted in a larger area of atherosclerotic plaque and induced atherosclerosis in an atherosclerotic mouse model[32]. This can be explained by counterregulatory upregulation so a negative feedback loop in the upregulation of Cys-C to counteract the increased elastolysis activity.

In addition, a renal mechanism might be another potential link between increased Cys-C and CAD and its severity. Several studies have demonstrated that early renal dysfunction is a strong and independent risk for CAD[37,38]. Systemic microinflammation response would accelerate the progression of atherosclerosis in CAD patients with early renal impairment. The systemic microinflammatory response has been found to accelerate the progression of atherosclerosis in CAD patients with early renal failure[39].

In this study, high serum Cys-C levels were found to be consistent with a high SYNTAX score. This suggests that Cys-C has an active role in the biological process that leads to the instability and formation of atherosclerotic plaque and therefore, Cys-C level may be a promising clinical biomarker to predict the severity and prognosis of CAD.

The most significant limitation of our study was that it was a cross-sectional study with a small number of patients. Secondly, only patients with a diagnosis of STEMI were

included in the study, and other patients with acute coronary syndrome were not evaluated. Finally, there was no control group with normal coronary arteries in our study. We believe that prospective studies with larger populations are needed to confirm our findings.

CONCLUSION

Our findings show that Cys-C levels are higher in those with severe CAD than in those with mild CAD and are significantly related to CAD severity. This implies that Cys-C may be an independent predictor of CAD severity, as verified by the SYNTAX score. Further research is needed to clarify the pathophysiological mechanisms responsible for this association.

Ethics Committee Approval: The study was approved by the ethics committee of Harran University Clinical Research Ethics Committee (Decision no: 22/03/02, Date: 07.02.2022). and was performed in accordance with the guidelines of the Declaration of Helsinki.

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - KT; Analysis/Interpretation - KT; Data Collection - KT; Writing - KT; Critical Revision - KT; Final Approval - KT; Statistical Analysis - KT; Overall Responsibility - KT.

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REFERENCES

1. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol 2019;234:16812-23. [Crossref]
2. Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. Curr Opin Nephrol Hypertens 2015;24:295-300. [Crossref]
3. van der Laan SW, Fall T, Soumaré A, Teumer A, Sedaghat S, Baumert J, et all. Cystatin C and cardiovascular disease: A Mendelian randomization study. J Am Coll Cardiol 2016;68:934-45. [Crossref]
4. Levin A, Lan JH. Cystatin C and cardiovascular disease: Causality, association, and clinical implications of knowing the difference. J Am Coll Cardiol 2016;68:946-8. [Crossref]
5. Shlofmitz E, Kuku KO, Waksman R, Garcia-Garcia HM. Intravascular ultrasound-guided drug-eluting stent implantation. Minerva Cardioangiol 2019;67(4):306-17. [Crossref]
6. Medical Advisory Secretariat. Intravascular ultrasound to guide percutaneous coronary interventions: An evidence-based analysis. Ont Health Technol Assess Ser 2006;6:1-97.
7. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX score: An angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-27.
8. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41:255-323. [Crossref]
9. Jones NR, McCormack T, Constanti M, McManus RJ. Diagnosis and management of hypertension in adults: NICE guideline update 2019. Br J Gen Pract 2020;70:90-1. [Crossref]
10. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77. [Crossref]
11. Kern M. What is the SYNTAX score and how should we use it? Cath Lab Digest 2009;17:(8).
12. Nakamura M. Angiography is the gold standard and objective evidence of myocardial ischemia is mandatory if lesion severity is questionable. - Indication of PCI for angiographically significant coronary artery stenosis without objective evidence of myocardial ischemia (Pro)-. Circ J 2011;75:204-10. [Crossref]
13. Bundhun PK, Sookharee Y, Bholee A, Huang F. Application of the SYNTAX score in interventional cardiology: A systematic review and meta-analysis. Medicine (Baltimore) 2017;96:7410 [Crossref]
14. Safarian H, Alidoosti M, Shafiee A, Salarifar M, Poorhosseini H, Ne matipour E. The SYNTAX score can predict major adverse cardiac events following percutaneous coronary intervention. Heart views 2014;15:99-105. [Crossref]
15. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. Exp Clin Cardiol 2002;7:40-53
16. Kleber ME, Goliasch G, Grammer TB, Pilz S, Tomaschitz A, Silbernagel G, et al. Evolving biomarkers improve prediction of long-term mortality in patients with stable coronary artery disease: the BIO-VILCAD score. J Intern Med 2014;276:184-94. [Crossref]
17. Jernberg T, Lindahl B, James S, Larsson A, Hansson LO, Wallentin L. Cystatin C: A novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. Circulation 2004;110:2342-8. [Crossref]
18. Negrusz-Kawecka M, Poręba R, Hulok A, Sciborski K, Marczak J, Bańkowski T. Evaluation of the significance of cystatin C levels in patients suffering from coronary artery disease. Adv Clin Exp Med 2014;23:551-8. [Crossref]
19. Koc M, Batur MK, Karaarslan O, Abali G. Clinical utility of serum cystatin C in predicting coronary artery disease. Cardiol J 2010;17:374-80.
20. Ichimoto E, Jo K, Kobayashi Y, Inoue T, Nakamura Y, Kuroda N, et al. Prognostic significance of cystatin C in patients with ST-elevation myocardial infarction. Circ J 2009;73:1669-73. [Crossref]
21. Yang H, Zhang L, Xu CH. Use of the SYNTAX Score II to predict mortality in interventional cardiology: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e14043. [Crossref]
22. Chichareon P, Onuma Y, van Klaveren D, Modolo R, Kogame N, Takahashi K, et al. Validation of the updated logistic clinical SYNTAX score for all-cause mortality in the GLOBAL LEADERS trial. EuroIntervention 2019;15:e539-e546. [Crossref]
23. Woitas RP, Kleber ME, Meinitzer A, Grammer TB, Silbernagel G, Pilz S, et al. Cystatin C is independently associated with total and cardiovascular mortality in individuals undergoing coronary angiography. The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Atherosclerosis 2013;229:541-8. [Crossref]
24. Pan J, Sun X, Zhang P, Chen H, Lin J. Relationship between serum cystatin-C and coronary lesion severity in coronary artery disease patients with a normal glomerular filtration rate. J Int Med Res 2021;49:300060520985639. [Crossref]
25. Lee M, Saver JL, Huang WH, Chow J, Chang KH, Ovbiagele B. Impact of elevated cystatin C level on cardiovascular disease risk in predominantly high cardiovascular risk populations: A meta-analysis. Circ Cardiovasc Qual Outcomes 2010;3:675-83. [Crossref]

26. Yang S, Song L, Zhao L, Dong P, Lai L, Wang H. Predictive value of cystatin C in people with suspected or established coronary artery disease: A meta-analysis. Atherosclerosis 2017;263:60-7. [Crossref]
27. Ristiniemi N, Lund J, Tertti R, Christensson A, Ilva T, Porela P, et al. 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. [Crossref]
28. Niccoli G, Conte M, Della Bona R, Altamura L, Siviglia M, Dato I, et al. Cystatin C is associated with an increased coronary atherosclerotic burden and a stable plaque phenotype in patients with ischemic heart disease and normal glomerular filtration rate. Atherosclerosis 2008;198:373-80. [Crossref]
29. Zi M, Xu Y. Involvement of cystatin C in immunity and apoptosis. Immunol Lett 2018;196:80-90. [Crossref]
30. Popović P, Dincić D, Popović-Milatović A, Banović T, Drasković-Pavlović B. Imunski i inflamatorni aspekti ateroskleroze [Immunologic and inflammatory aspects of atherosclerosis]. Vojnosanit Pregl 2000;57:89-98.
31. Nasonov EL, Paniukova EV, Aleksandrova EN. S-reaktivnyĭ belok--marker vospaleniia pri ateroskleroze (novye dannye) [C-reactive protein--marker of inflammation in atherosclerosis (new data)]. Kardiologiia 2002;42:53-62.
32. Bengtsson E, To F, Grubb A, Håkansson K, Wittgren L, Nilsson J, et al. 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. [Crossref]
33. Liu J, Sukhova GK, Sun JS, Xu WH, Libby P, Shi GP. Lysosomal cysteine proteases in atherosclerosis. Arterioscler Thromb Vasc Biol 2004;24:1359-66. [Crossref]
34. Ge C, Ren F, Lu S, Ji F, Chen X, Wu X. Clinical prognostic significance of plasma cystatin C levels among patients with acute coronary syndrome. Clin Cardiol 2009;32:644-8. [Crossref]
35. Windhausen F, Hirsch A, Fischer J, van der Zee PM, Sanders GT, van Straalen JP, et al. Cystatin C for enhancement of risk stratification in non-ST elevation acute coronary syndrome patients with an increased troponin T. Clin Chem 2009;55:1118-25. [Crossref]
36. Yang H, Wang C, Guo M, Zhou Y, Feng Z, Yin Z. Correlations between peroxisome proliferator activator receptor γ, cystatin C, or advanced oxidation protein product, and atherosclerosis in diabetes patients. Pathol Res Pract 2015;211:235-9. [Crossref]
37. Bengtsson E, To F, Grubb A, Håkansson K, Wittgren L, Nilsson J, et al. 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. [Crossref]
38. Qi L, Liu H, Cheng L, Cui C, Chen X, Yang S, et al. Impact of renal insufficiency on prognosis of patients with acute coronary syndrome. Int J Gen Med 2021;14:8919-8927. [Crossref]
39. Arboix A, Miguel M, Císcar E, García-Eroles L, Massons J, Balcells M. Cardiovascular risk factors in patients aged 85 or older with ischemic stroke. Clin Neurol Neurosurg 2006;108:638-43. [Crossref]
40. Kaneko R, Sawada S, Tokita A, Honkura R, Tamura N, Kodama S, et al. Serum cystatin C level is associated with carotid arterial wall elasticity in subjects with type 2 diabetes mellitus: A potential marker of early-stage atherosclerosis. Diabetes Res Clin Pract 2018;139:43-51. [Crossref]