INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2023.09326
Int J Med Biochem 2024;7(1):18–25

Research Article

The association of serum proprotein convertase furin/PCSK3 concentrations with stable coronary artery disease and coroner artery lesion severity

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Abstract

Objectives: Furin (Proprotein Convertase Subtilisin/Kexin Type 3, PCSK3) is a proprotein convertase involved in the processing of precursor proteins. Furin substrates play significant roles in the initiation and progression of atherosclerosis, which is the primary cause of coronary artery disease (CAD). This study aimed to investigate the serum furin concentrations in stable CAD patients and their relationship with disease severity.

Methods: The study included 81 stable CAD patients and 50 subjects without coronary artery lesions. Coronary angiography was performed via the percutaneous femoral artery approach, and the severity of CAD was assessed using the Gensini score. Serum furin concentrations were measured using an enzyme-linked immunosorbent assay.

Results: Serum furin concentrations were significantly higher in CAD patients compared to CAD-negative subjects (p=0.0001). The serum furin levels of mild, moderate, and severe CAD patients were 1.53 ng/mL, 2.01 ng/mL, and 3.03 ng/mL, respectively, which were significantly different from CAD-negative subjects (p=0.018, p=0.002, and p=0.0001, respectively). Furin levels were found to be an independent predictor of CAD and exhibited potential diagnostic value for CAD and severe CAD.

Conclusion: The study concluded that serum furin concentrations could be considered a new risk factor for CAD, in addition to well-known biomarkers.

Keywords: Atherosclerosis, coronary arteries, dibasic processing enzyme, paired basic amino acid cleaving enzyme, proprotein convertases

How to cite this article: Balaban Yucesan F, Orem A, Orem C, Ilter A, Ozer Yaman S, Yaman H, et al. The association of serum proprotein convertase furin/PCSK3 concentrations with stable coronary artery disease and coroner artery lesion severity. Int J Med Biochem 2024;7(1):18–25.

Cardiovascular diseases (CVDs) continue to be the most important health problem and are the leading cause of death globally [1]. CVDs are a group of disorders of the heart and blood vessels including coronary artery disease (CAD). The main cause of CAD is atherosclerosis, which is a complex pathophysiological process mainly driven by endothelial dysfunction, lipid accumulation, and inflammation [2]. While traditional risk factors including dyslipidemia, hypertension, diabetes mellitus contribute to the pathogenesis of CAD, other novel risk factors may be involved. The proprotein convertases

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Submitted: July 24, 2023 **Accepted:** August 31, 2023 **Available Online:** January 09, 2024

(PCs) are serine proteases involved in the processing of precursor proteins; they often are responsible for the activation of their substrates but sometimes lead to inactivation [3, 4]. PCs are generally abbreviated as PCSK because of their similarity with bacterial subtilisin and yeast kexin proteases [5], and the genes encoding these enzymes are called *PCSKs* [6]. There are nine mammalian PC families: PC1/3, PC2, Furin, PC4, PC5/6, PACE4, PC7, SKI-1/S1P, and PCSK9 [4]. Furin (PCSK3) is the first endoprotease identified among the PCs and is expressed ubiquitously in all mammalian tissues and cell lines [7]. This PC is localized primarily in the trans-Golgi network (TGN) but can cycle between the TGN and the cell surface. Furin, a type-I membrane-bound protein, can be present in the extracellular milieu with ectodomain shedding from the membrane [8, 9]. There are many mammalian substrates of furin including cytokines, hormones, growth factors, receptors, and it also cleaves bacterial and viral substrates [5, 10]. Any dysfunction in the expression or activity of furin may be associated with a variety of disorders, such as atherosclerosis, cardiovascular diseases (CVDs), cancer, diabetes, infectious diseases, inflammation [5, 11–14]. In particular, the potential targets of furin are involved in the initiation and progression of atherosclerosis by regulating lipid and lipoprotein metabolism, inflammatory response, blood pressure, and formation of atherosclerotic lesions [11, 15]. In recent years, it has been shown that the expression of furin and PCSKs5-7 is associated with key molecular pathways and mechanistic networks for CVD [12]. Also, it has been observed that furin is among the proprotein convertases with the highest novel CVD therapeutic potential [12], and it would be important to determine the exact role of furin in CAD pathogenesis as a new target for the treatment of the disease.

To the best of our knowledge, studies focusing on the clinical use of furin as a biomarker for CAD are insufficient. We hypothesized that furin might be a circulating candidate biomarker for CAD and its level could be related to coronary artery lesion severity. The aim of the present study was to investigate the serum level of furin protease in subjects with CAD and to evaluate the relationship between its concentration and the severity of coronary artery disease determined by Gensini score.

Materials and Methods

Study population

The study population consisted of eighty-one (81) stable coronary artery disease patients who were diagnosed by coronary angiography [CAD (+)] and fifty (50) individuals who did not have a lesion in their coronary arteries [CAD (–)], who applied to the outpatient clinic of Karadeniz Technical University Faculty of Medicine, Department of Cardiology. A detailed anamnesis from all subjects was taken, and physical examinations were performed before coronary angiography. Individuals younger than 18 years of age, who had malignant neoplasm, severe renal/hepatic disease, systemic infection, recent history of surgery, or were pregnant were excluded from the study. An informed consent form was signed by the individuals participating in the study. Ethics committee approval was obtained for the research from the Karadeniz Technical University (KTU) Faculty of Medicine Scientific Researches Ethics Committee (Submission number: 2011/3, approval date: October 17, 2011) and was in accordance with the Declaration of Helsinki.

Gensini score

Coronary angiography was performed for all individuals via the percutaneous femoral artery approach following the standard procedure [16]. The Gensini score [17] was used to assess the severity of coronary artery disease. Gensini scores were determined using the following steps: 1. Definition of the concentric or eccentric luminal narrowing degrees; 1 point for ≤25% stenosis, 2 points for 26–50% stenosis, 4 points for 51–75% stenosis, 8 points for 76–90% stenosis, 16 points for 91–99% stenosis, and 32 points for 100% occlusion. 2. Definition of the coronary artery lesion site; 5 points for the left main coronary artery, 2.5 points for the proximal left anterior descending branch and left circumflex artery, 1.5 points for midsegment of the left anterior descending coronary artery, 1 point for the diagonal branch and obtuse marginal branches, and 0.5 points for the second diagonal and left circumflex artery posterolateral branch. 3. The summation of the individual coronary segment scores (the narrowing scores were multiplied by a coefficient defined for each main coronary artery and each segment). The CAD (+) patients were classified into three groups according to the tertile of their Gensini score: Mild (Gensini score 2–7.5 points), moderate (Gensini score 8–35.5 points), and severe (Gensini score 36–177 points).

Biochemical analyses

Blood samples were obtained from an antecubital vein of each subject into the serum separator tubes without anticoagulant. Serum samples were separated after centrifugation at 1800g for 10 min and stored at –80°C until analysis. Serum concentrations of glucose, triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) were measured enzymatically using a Roche/cobas 6000 series clinical chemistry analyzer (Mannheim, Germany). Serum hs-CRP concentrations were assigned by a latex-enhanced immunonephelometric method on a Siemens Dade Behring BN II nephelometer (Marburg, Germany). The measurement of serum hs-TroponinT concentrations was determined by an Electrochemiluminescence (ECL) method on a Roche Elecsys 2010 (Mannheim, Germany). The original reagents of the analyzers were used to measure the concentrations of variables. The quantification of these variables was carried out in the Medical Biochemistry Laboratory of Farabi Hospital at Karadeniz Technical University Faculty of Medicine after daily quality control procedures were completed. Serum furin concentrations were determined by using an enzyme-linked immunosorbent assay kit (Human furin USCN Life Science Inc., Wuhan, PRC) and expressed as ng/mL. The minimum

Table 1. Demographic, anthropometric and biochemical variables in CAD (-) and CAD (+) subjects

Variables	CAD (-) n=50		CAD (+) n=81		p
	n	%	n	%	
Age, years	58±14		62±12		0.043*
Male,	16	32	65	80	0.0001**
Hypertension	24	48	41	51	0.771**
Diabetes mellitus	2	4	18	22	0.005**
Smoking	2	4	18	22	0.005**
Family history	21	42	36	44	0.878**
BMI, kg/m^2	28 (26–32)		29 (26–32)		0.636
Waist cimcumference, cm	100 (90–106)		102 (94–110)		0.293
SBP, mm/Hg	120 (110–136)		125 (118–133)		0.703
DBP, mm/Hg	78 (60–80)		78 (68–80)		0.710
Heart rate, beats/min	70 (68–75)		72 (65–78)		0.738
TC, mg/dL	173±37		167±42		0.399*
LDL-C, mg/dL	123±30		120±38		0.694*
HDL-C, mg/dL	41.5±10.4		36±6.67		0.001*
TG, mg/dL	106 (83–163)		133 (93.5–167)		0.348
Glucose, mg/dL	94 (82.8–110)		98 (85.5–149)		0.076
Furin, ng/mL	1.00 (0.65–2.20)		2.11 (1.17–3.50)		0.0001
Hs-TroponinT, ng/L	6 (4–11)		9 (7–18)		0.001
Hs-CRP, mg/L	0.28 (0.11–0.63)		0.34 (0.15–0.79)		0.287

*: p for Independent t-test and values are given as mean±standard deviation; **: p for Pearson Chi-Square Test and values are given as n (%). The remaining variables are given as median with IQR(Q1-Q3) and Mann-Whitney U Test was used for statistical analysis. CAD: Coronary artery disease; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; Hs-CRP: High sensitive-C reactive protein.

detectable dose of the assay is less than 0.055 ng/mL with an intra-assay CV% of <10% and an inter-assay CV% of <12%.

Statistical analyses

The Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. The data were presented using mean and standard deviation (mean±SD) for normally distributed variables. The data not scattered normally were expressed as median with interquartile range (Q1-Q3) values. The independent t-test was used to compare the variables that showed normal distribution. Pairwise comparisons were made using the Mann-Whitney U test for non-normal distribution. The data comparisons for mild, moderate, and severe CAD (+) patients were performed by the Kruskal-Wallis test. The Chi-Square test was used for categorical variables. Binary logistic regression analysis was performed to determine independent predictors of CAD. A binary logistic regression model was established using age, gender, diabetes mellitus, smoking, HDL-C, and furin that were significant in the univariate analysis as independent variables. The model's goodness of fit was evaluated using the Hosmer-Lemeshow test. The correlation coefficients (r) and their significance were assessed by Pearson correlation analysis, and log transformation was performed for non-normally distributed variables. Statistical analyses were performed using SPSS version 23.0 software (SPSS, Inc., Chicago, USA). Receiver operating characteristics (ROC) curves were constructed on MedCalc version 9.6.4 software (MedCalc Software BVBA, Belgium) to assess sensitivity, specificity, and respective areas under the curves (AUCs) with 95% CI. P-values <0.05 were considered statistically significant.

Results

The main characteristics of demographic, anthropometric, and biochemical variables of the study population are represented in Table 1. The mean age of CAD (–) subjects was 58±14 years, and the mean age of CAD (+) patients was 62±12 years (p=0.043). Male individuals constituted 80% of CAD (+) patients and were significantly different from CAD (–) subjects (p=0.0001). The body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate values were not different between CAD (+) patients and CAD (–) subjects. The history of diabetes mellitus and smoking was found to be higher in CAD (+) patients (p=0.005). In addition, no significant difference was found in fasting TC, LDL-C, TG, and glucose levels, but HDL-C levels showed a significant decrease in CAD (+) patients (p=0.001). The median serum furin concentration in CAD (+) patients (2.11 ng/mL) was approximately twofold higher compared to CAD (–) subjects (1.00 ng/mL) (p=0.0001) (Table 1 and Fig. 1a). Hs-TroponinT concentration was found to be significantly

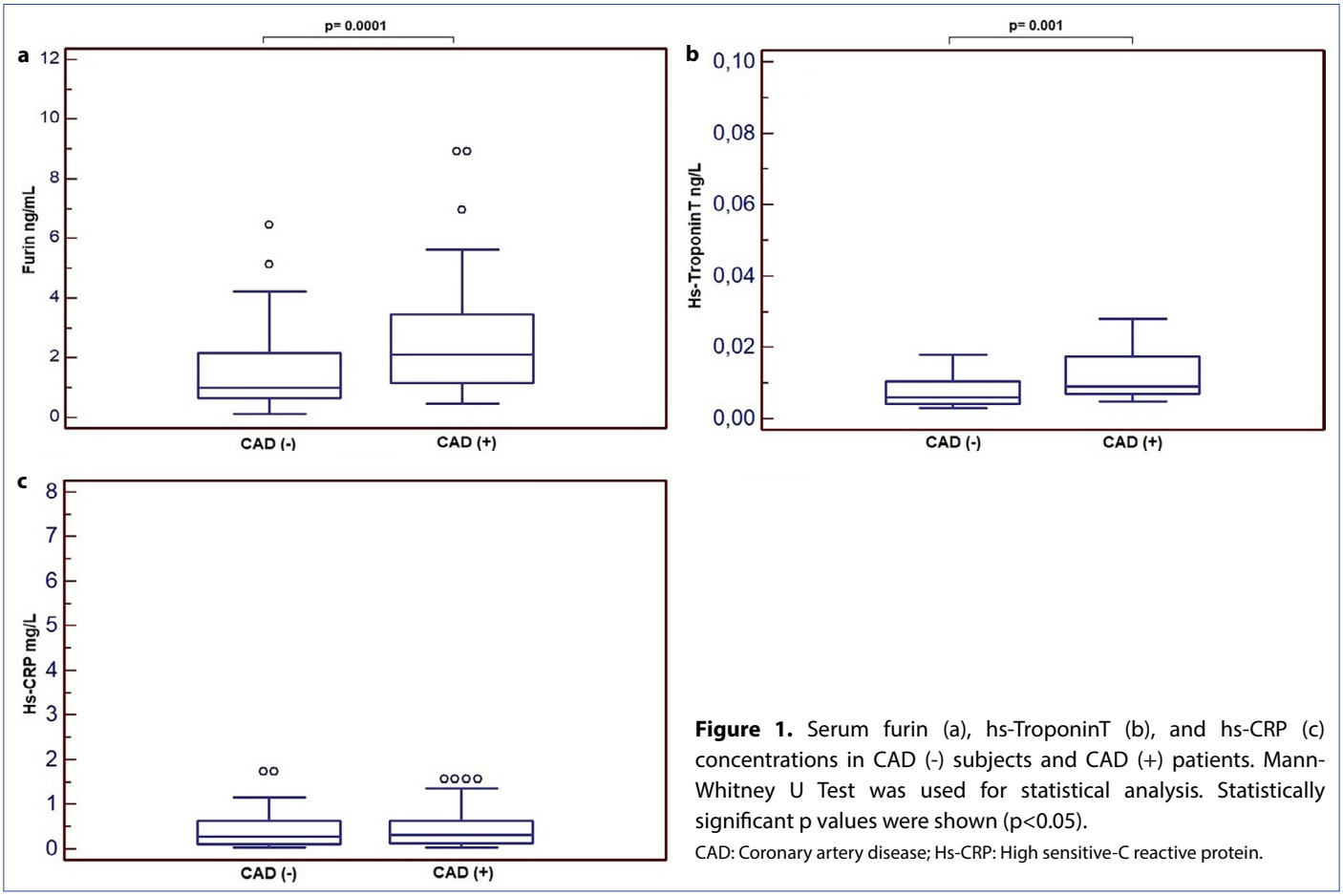


Figure 1. Serum furin (a), hs-TroponinT (b), and hs-CRP (c) concentrations in CAD (-) subjects and CAD (+) patients. Mann-Whitney U Test was used for statistical analysis. Statistically significant p values were shown (p<0.05).

CAD: Coronary artery disease; Hs-CRP: High sensitive-C reactive protein.

higher in CAD (+) patients versus CAD (–) subjects (p=0.001) (Table 1 and Fig. 1b). Although there was an increase in hs-CRP concentrations in CAD (+) patients, it did not reach a statistically significant level (p=0.287) (Table 1 and Fig. 1c).

In order to assess the potential of serum furin concentrations to discriminate between CAD (+) patients and CAD (–) subjects, ROC curve analysis was performed. The ROC curves for furin, hs-TnT, and hs-CRP were evaluated, and the area under the curve (AUC) values, 95% confidence intervals (CI), and p-values were provided in Figure 2. Serum furin concentrations had significant discriminating ability between CAD (+) patients and CAD (–) subjects with the highest AUC value of 0.730 (95% CI=0.646–0.804, p=0.0001). In addition, the serum furin cut-off value corresponding to the maximum of the Youden index was 1.03 ng/mL (86.4% sensitivity, 54% specificity).

The results of the binary logistic regression analysis for CAD risk factors are presented in Table 2. The analysis showed that serum furin concentrations (OR=1.399, 95% CI=1.075–1.822, p=0.013), gender (OR=7.322, 95% CI=2.767–19.376, p=0.001), and age (OR=1.040, 95% CI=1.003–1.078, p=0.034) were independent predictors for CAD.

CAD (+) patients were divided into tertiles as mild, moderate, and severe according to their Gensini scores (Table 3). The median furin levels of mild, moderate, and severe CAD (+) patients were 1.53 ng/mL, 2.01 ng/mL, and 3.03 ng/mL, respectively (Table 3).

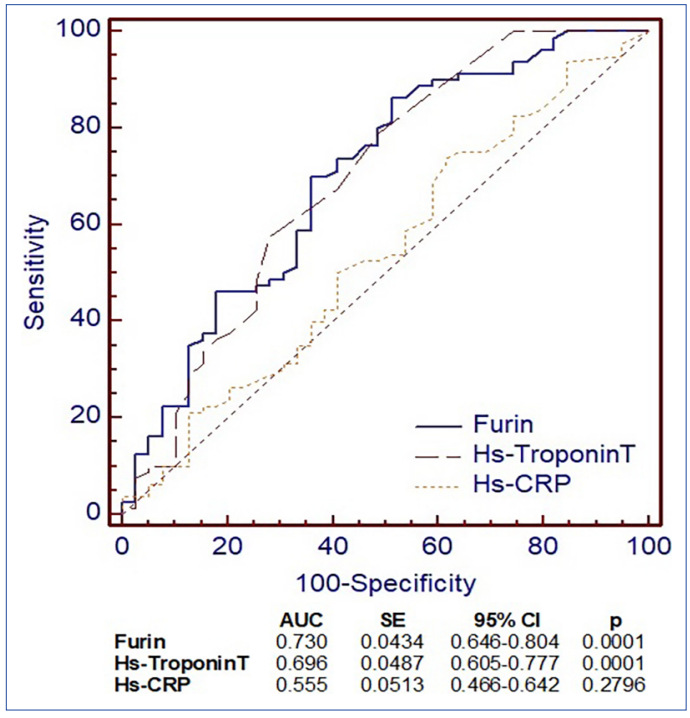


Figure 2. Receiver operating characteristic curve of furin, hs-TroponinT and hs-CRP concentrations for discrimination of CAD (+) patients from CAD (-) subjects.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for coronary artery disease by using binary logistic regression analysis

Variables	OR	95% CI	p
Gender	7.322	2.767–19.376	0.001
Furin	1.399	1.075–1.822	0.013
Age	1.040	1.003–1.078	0.034
Diabetes mellitus	5.178	0.957–28.024	0.056
Smoking	2.888	0.565–14.762	0.203
HDL-C	0.967	0.912–1.025	0.254

Although it tended to increase, it was not statistically significant among tertiles (p=0.131). On the other hand, the serum furin levels of mild, moderate, and severe CAD (+) patients were found significant according to CAD (–) subjects (p=0.018, p=0.002, and p=0.0001, respectively, Fig. 3a). Moreover, hs-TroponinT concentrations of mild, moderate, and severe CAD (+) patients were found significant according to CAD (–) subjects (p=0.025, p=0.006, and p=0.002, respectively, Fig. 3b), but hs-CRP levels of the tertiles were not significant compared to CAD (–) subjects (p>0.05, Fig. 3c). There were no statistically significant alterations between the tertiles in terms of other variables (Table 3).

The results of ROC curve analysis of the potential diagnostic value of serum furin concentrations for severe CAD patients were provided in Figure 4. For the analysis, mild+moderate CAD patients (n=54) were considered as one group. Serum furin levels had discriminating ability between severe CAD patients and mild+moderate CAD patients (AUC=0.635, 95% CI=0.520–0.739, p=0.045). The serum furin cut-off point corresponding to the maximum of the Youden index was 2.61 ng/mL (59.3% sensitivity, 74.1% specificity).

The associations between serum furin levels and other variables were also evaluated. In the whole study population, we observed a positive correlation between serum furin levels and hs-CRP levels (r=0.179, p=0.041), but serum furin levels showed a negative correlation with serum HDL-C levels (r=–0.203, p=0.020). Moreover, furin levels did not correlate with the Gensini score in CAD (+) subjects (r=0.091, p=0.420).

Discussion

The main findings of the present study were that the concentrations of serum furin increased in stable CAD patients and showed a tendency to increase with coronary artery lesion severity.

There were limited investigations about circulating furin levels in CAD patients. To our knowledge, there is only one study examining plasma furin levels in stable CAD patients. This study by Langnau et al. [18] focused on the association between plasma furin levels and the prognosis of COVID-19 patients with preexisting stable CAD. Additionally, they did not observe any difference in furin levels between healthy controls (n=39) and stable CAD patients (n=28) [18]. We observed

Table 3. Demographic, anthropometric and biochemical variables according to Gensini score tertiles in CAD (+) patients

Variables	Mild n=27		Moderate n=27		Severe n=27		p
	n	%	n	%	n	%	
Age, years	62 (53–70)		62 (53–68)		64 (55–70)		0.751
Male	19	70	24	89	22	82	0.228*
Hypertension	14	52	13	48	14	52	0.952*
Diabetes Mellitus	3	11	9	33	6	22	0.145*
Smoking	8	30	7	26	3	11	0.223*
Family history	13	48	9	33	14	52	0.377*
BMI, kg/m^2	27 (25–32)		29 (25–32)		29 (27–32)		0.444
Waist cimcumference, cm	105 (90–110)		102 (95–110)		100 (94–108)		0.952
SBP, mm/Hg	125 (120–130)		120 (110–130)		130 (120–140)		0.312
DBP, mm/Hg	80 (75–80)		70 (65–80)		70 (65–80)		0.028
Heart rate, beats/min	72 (67–76)		68 (60–78)		71 (65–82)		0.503
TC, mg/dL	167 (153–191)		154 (127–175)		162 (138–190)		0.174
LDL-C, mg/dL	127 (104–138)		106 (85–134)		115 (104–142)		0.176
HDL-C, mg/dL	36 (31–41)		36 (31–39)		36 (29–44)		0.898
TG, mg/dL	124 (81–154)		136 (109–167)		136 (88–179)		0.724
Glucose, mg/dL	95 (86–122)		102 (89–166)		90 (83–149)		0.409
Furin, ng/mL	1.53 (1.05–3.37)		2.01 (1.17–2.61)		3.03 (1.45–3.87)		0.131
Hs-TroponinT, ng/L	6 (9–18)		7 (9–17)		7 (11–18)		0.629
Hs-CRP, mg/L	0.25 (0.12–0.52)		0.33 (0.21–0.63)		0.46 (0.18–1.36)		0.206

*: p for Pearson Chi-Square Test and values are given as n (%). The remaining variables are given as median with IQR(Q1-Q3) and Kruskal Wallis Test was used for statistical analysis.

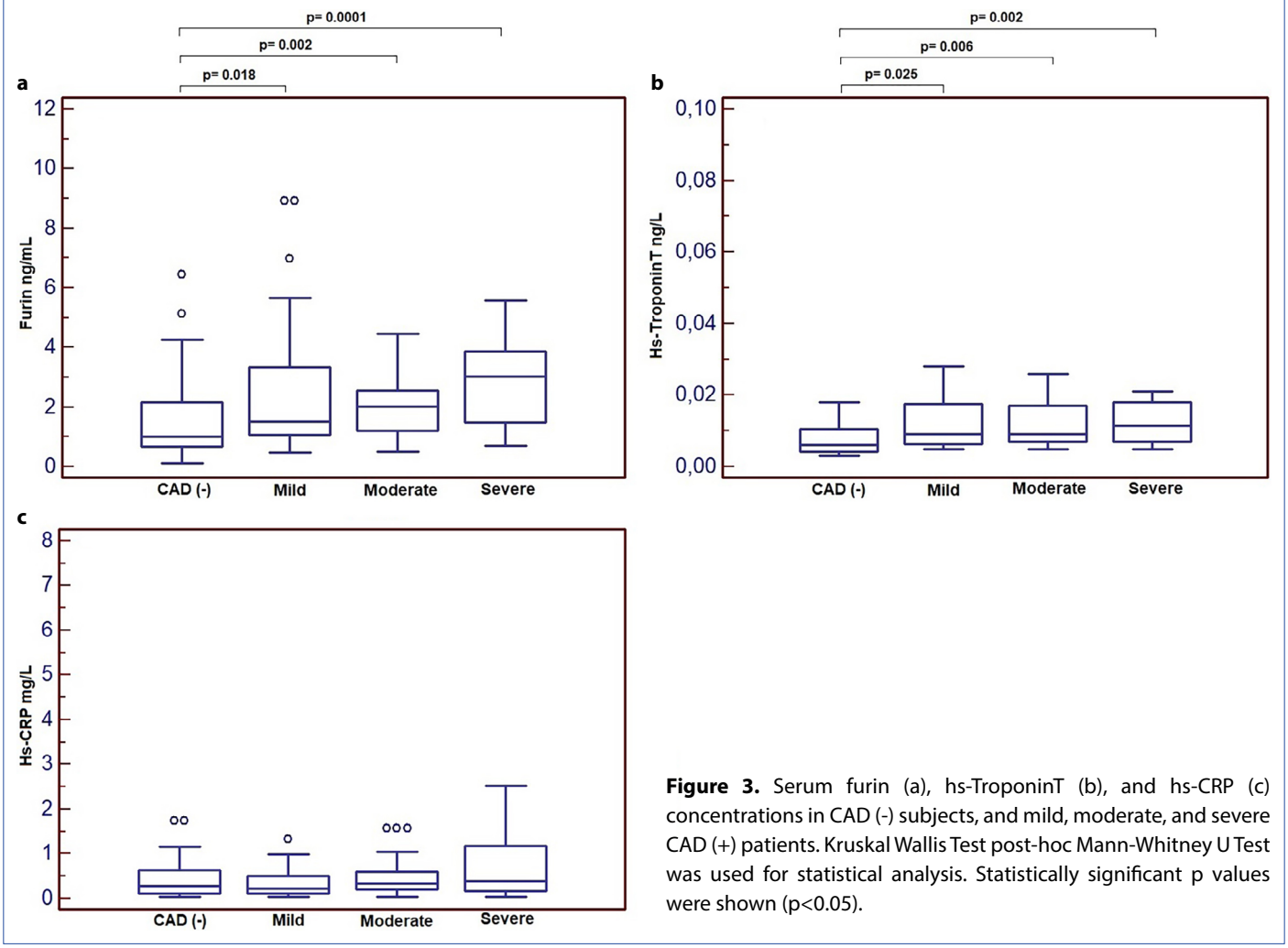
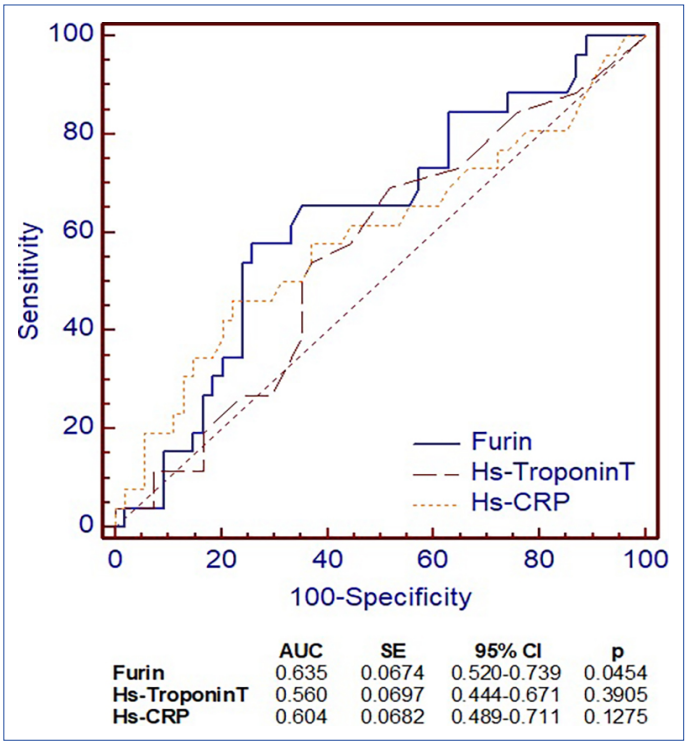


Figure 3. Serum furin (a), hs-TroponinT (b), and hs-CRP (c) concentrations in CAD (-) subjects, and mild, moderate, and severe CAD (+) patients. Kruskal Wallis Test post-hoc Mann-Whitney U Test was used for statistical analysis. Statistically significant p values were shown ($p<0.05$).

approximately twofold increased serum furin levels in stable CAD patients compared to CAD (–) subjects. The difference in findings may be due to the characteristics of the study population. In the current study, the increased serum furin levels in CAD patients might be explained by its increased cellular activity. Furin has roles in the transformation of many zymogen substrates to their functionally active form, which participate in atherogenesis, and thus CAD. Furin modulates lipid metabolism by inactivating endothelial lipase (EL) [19] and lipoprotein lipase (LPL) [20]. It regulates plasma LDL-C levels by cleaving PCSK9 [21]. Furin promotes the activation of pro-inflammatory tumor necrosis factor (TNF) superfamily cytokines [22], is involved in the MT1-MMP driven proteolytic cascade of pro-MMP2 activation [23], and regulates blood pressure by cleaving the (pro)renin receptor [24]. Thus, furin is an important regulator of cell functions associated with the initiation and progression of atherosclerosis [11]. In the present study, ROC curve analysis of furin for stable CAD patients showed discriminating power, and its value was better than hs-TnT. Also, binary logistic regression analysis indicated that serum furin concentrations, gender, and age were independent predictors for CAD. Therefore, it could be proposed that increased levels of furin may indicate progression of atherosclerosis and serve as an independent predictor for CAD risk.

When evaluating furin levels in relation to coronary artery lesion severity, there was a tendency for serum furin levels to increase from the bottom tertile to the upper tertile. One of the most important findings of the current study was that severe CAD patients had the highest serum furin levels. Furthermore, serum furin levels discriminated severe CAD patients from mild and moderate CAD patients. These findings may be clinically important because of the potential role of furin as a circulating biomarker of coronary artery disease lesion severity. However, in the current study, serum furin levels did not correlate with the Gensini score in CAD patients. Wang et al. [25] investigated the prognostic value of furin in acute myocardial infarction (AMI) patients [25]. They observed that patients with higher furin levels had an increased risk of major adverse cardiac events (MACE), all-cause mortality, recurrent MI, and hospitalization for heart failure. Conversely, another study found that plasma furin was not associated with the risk of MACE, but higher levels of plasma furin might be related to a higher risk of recurrent MI in AMI patients [26]. Moreover, Liu et al. [26] found a slight increase in cTNT levels in patients with higher



	AUC	SE	95% CI	p
Furin	0.635	0.0674	0.520-0.739	0.0454
Hs-TroponinT	0.560	0.0697	0.444-0.671	0.3905
Hs-CRP	0.604	0.0682	0.489-0.711	0.1275

Figure 4. Receiver operating characteristic curve of furin, hs-TroponinT and hs-CRP concentrations for discrimination of severe CAD (+) patients from mild and moderate CAD (+) patients.

plasma furin concentrations. They suggested that higher circulating furin concentrations may imply progression of atherosclerosis and more severe or vulnerable plaque lesions.

The main limitation of the current study was that the number of CAD patients in tertiles was small. Further studies with larger sample sizes on the clinical effectiveness of using furin as a circulating biomarker for CAD risk and prognosis need to be conducted.

It was concluded that serum furin levels were increased in stable CAD patients, predicted CAD risk, and discriminated the severity of CAD. Therefore, furin might be used as a candidate molecule for determining CAD risk.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The Karadeniz Technical University Faculty of Medicine Scientific Researches Ethics Committee (No: 2011/3, Date: 17/10/2011).

Financial Disclosure: This research work was supported by the Research Fund of Karadeniz Technical University, Project Number: 5832.This research did not receive funds to cover publication costs.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – F.B.Y., A.O.; Design – F.B.Y., A.O., C.O., A.I.; Supervision – F.B.Y., A.O.; Funding – F.B.Y.; Materials – F.B.Y., C.O., A.I., H.Y., B.A., T.M.S.; Data collection &/or processing – F.B.Y., C.O., A.I., S.O.Y., B.A., H.Y., T.M.S.; Analysis and/or interpretation – F.B.Y., A.O., C.O., S.O.Y.; Literature search – F.B.Y., S.O.Y.; Writing – F.B.Y., A.O.; Critical review – F.B.Y., A.O., C.O., A.I., S.O.Y., H.Y., B.A., T.M.S.

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