# Effects of glomerular filtration rate on the severity of coronary heart disease

## Glomerül filtrasyon hızının koroner kalp hastalığı şiddeti üzerine etkileri

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## ABSTRACT

***Objective:*** Chronic kidney disease (CKD) is considered to be one of the most common risk factors for cardiovascular diseases. Glomerular filtration rate (GFR) is the best method of testing level of kidney function and determining stage of kidney disease. The aim of this study was to examine the impact of renal function on severity of coronary heart disease (CHD).

***Methods:*** The present study included 918 patients undergoing elective coronary angiography. GFR was evaluated by simplified Modification of Diet in Renal Disease (MDRD) formula (mL/min/1.73 $m^2$). The extent and severity of CHD were evaluated according to SYNTAX score.

***Results:*** According to SYNTAX score, 416 patients had normal coronary arteries or nonsignificant CHD (control group), 267 had mild CHD (SYNTAX score: 1–22), 129 had moderate CHD (SYNTAX score: 23–32), and 106 had severe CHD (SYNTAX score: ≥33). Estimated GFR values (median [$25^{th}$–$75^{th}$ percentiles]) were 99.00 (83.00–116.00) in the control group, 85.00 (73.00–101.00) in the mild CHD group, 87.00 (73.25–101.75) in the moderate CHD group, and 81.00 (65.00–101.00) in the severe CHD group. According to Spearman's rank correlation analysis, a negative correlation found between MDRD and SYNTAX score was statistically significant ($p<0.001$, $r=-0.268$).

***Conclusion:*** Renal function is an important predictor of presence and severity of angiographic CHD in patients without severe renal impairment. Negative correlation between MDRD and SYNTAX score was determined. This simple biochemical test can be used in determining risk of cardiovascular disease aside from other risk factors during routine clinical practice.

## ÖZET

***Amaç:*** Kronik böbrek hastalığı, kardiyovasküler hastalıklar için en yaygın risk faktörlerinden biri olarak kabul edilir. Glomerül filtrasyon hızı (GFH), böbrek fonksiyonunun düzeyini ölçmek ve böbrek hastalığı evresini belirlemek için en iyi testtir. Bu çalışmanın amacı koroner kalp hastalığı (KKH) şiddeti üzerine böbrek fonksiyonunun etkisini araştırmaktır.

***Yöntemler:*** Bu çalışmaya elektif koroner anjiyografi yapılan 918 hasta alındı. GFH, MDRD (Modifcation of Diet in Renal Disease) formülü ile değerlendirildi (ml/dak/1.73 $m^2$). KKH derecesi ve şiddeti SYNTAX skoruna göre belirlendi.

***Bulgular:*** SYNTAX skoruna göre, hastaların 416'sında normal koroner arterler veya önemsiz derecede KKH (Kontroller); 267'sinde hafif derecede KKH (SYNTAX skoru: 1–22); 129'unda orta derecede KKH (SYNTAX skoru: 23–32) ve 106'sında ciddi derecede KKH (SYNTAX skoru ≥33) vardı. Tahmini GFH değerleri (ortanca [25.–75. yüzdelik]), kontrol grubunda 99.00 (83.00–116.00), hafif derecede KKH olan grupta 85.00 (73.00–101.00), orta derecede KKH olan grupta 87.00 (73.25–101.75) ve ciddi derecede KKH olan grupta 81.00 (65.00–101.00) idi. Spearman korelasyon analizine göre, MDRD ve SYNTAX skoru arasında istatistiksel olarak anlamlı negatif korelasyon bulundu ($p<0.001$, $r=-0.268$).

***Sonuç:*** Böbrek fonksiyonu, ciddi böbrek yetersizliği olmayan hastalarda anjiyografik KKH varlığı ve şiddetinin önemli bir belirleyicisidir. MDRD ve SYNTAX skoru arasında negatif korelasyon saptandı. Bu nedenle, bu basit biyokimyasal test rutin klinik uygulama sırasında diğer risk faktörlerinin yanı sıra, kardiyovasküler hastalık riskini belirlemede kullanılabilir.

Cardiovascular diseases are the leading cause of death worldwide in end-stage renal disease (ESRD) populations. In patients with chronic kidney disease (CKD), cardiovascular risk is, at least in part, mediated by vascular stiffening. However, cardiovascular risk is not limited to ESRD, and risk of cardiovascular mortality begins to increase with even mild impairment of renal function.[1] Decreased renal function is associated with higher incidence of atherosclerotic process and mortality from cardiovascular dis-

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orders.[2] Estimated glomerular filtration rate (eGFR) is a widely accepted, useful, easily calculated, and reproducible parameter used to assess renal functional status. It has been reported that eGFR is more useful than serum creatinine as a predictor of outcomes.[3] The aim of this study was to investigate the relationship between angiographic severity, complexity of coronary heart disease (CHD) and eGFR, which was calculated according to Modification of Diet in Renal Disease (MDRD) formula.[4]

**Abbreviations:**

| | |
|---|---|
| *CHD* | *Coronary heart disease* |
| *CKD* | *Chronic kidney disease* |
| *DM* | *Diabetes mellitus* |
| *eGFR* | *Estimated glomerular filtration rate* |
| *ESRD* | *End-stage renal disease* |
| *GFR* | *Glomerular filtration rate* |
| *MDRD* | *Modification of diet in renal disease* |
| *PCI* | *Percutaneous coronary intervention* |

## METHODS

The sample was derived from a population of 1,321 consecutive patients who underwent coronary angiography due to positive noninvasive stress test. In total, 403 were excluded because they met the exclusion criteria (n=314) and did not fulfill the inclusion criteria (n=89). Finally, 918 patients were enrolled, with 563 male (61.3%) and 355 female (38.7%) subjects included. The study was approved by the institutional review board and informed consent was obtained from all patients. Inclusion criteria were age (>18 years), coronary angiogram clear enough to enable evaluation of cause of stress-induced chest pain, and patient's consent. Exclusion criteria were current pregnancy, cardiomyopathy, previous myocardial infarction or revascularization procedures, unstable angina pectoris, history of congenital renal disease, and hemodialysis.

Selective coronary angiography was performed by femoral approach using Judkins technique and Innova 3100 angiographic system (General Electric, Buc Cedex, France). Multiple views were obtained, with visualization of the left anterior descending and left circumflex coronary artery in at least 4 projections, and the right coronary artery in at least 2 projections. Coronary angiograms were recorded on compact discs in DICOM format. All angiograms were analyzed by 2 experienced cardiologists blinded to clinical data. Extent and severity of CHD were evaluated according to SYNTAX score, calculated by a program consisting of sequential and interactive self-guided questions. Algorithm consisted of 12 main questions. Total SYNTAX score was composed of individual scores for each lesion with a diameter stenosis of ≥50% in a vessel of ≥1.5 mm in diameter by visual assessment, as previously reported.[5] Patients were divided into 4 groups based on SYNTAX scores: control group (SYNTAX score: 0); mild CHD group (group I; SYNTAX score: 1–22); moderate CHD group (group II; SYNTAX score: 23–32); severe CHD group (group III; SYNTAX score: ≥33).

Complete blood count and biochemical examination of blood were performed in all patients before procedure. eGFR was calculated according to MDRD formula (eGFR [mL/min/1.73m$^2$]=186 x [creatinine/88.4]-1.154 x [Age]-0.203 x [0.742 if female, 1.210 if black]).[4] According to eGFR values (mL/min/1.73 m$^2$), patients were classified into 5 stages: stage I (eGFR≥90, 52.9%); stage II (90>eGFR≥60, 36.6%); stage III (60>eGFR≥30); stage IV (30>eGFR≥15); and stage V (15>eGFR). Stages III—V (eGFR<60 mL/min/1.73 m$^2$) were defined as CKD (10.5%).[3]

### Statistical analysis

Data were analyzed with SPSS software (version 21.0 for Windows; SPSS Inc., Chicago, IL, USA). Normal distribution of variables was verified with Kolmogorov-Smirnov test. Degrees of association between continuous variables were evaluated by Spearman's rank correlation analyses. Comparisons between the groups were performed with Kruskal-Wallis test and Mann-Whitney U test. When needed, binary comparisons among the groups were performed using Conover-Inman test ($p<0.05$ was considered statistically significant). A chi-square test was used to investigate whether distributions of categorical variables differed within groups. An optimal cutoff value to predict significant CHD by eGFR was determined by receiver operating characteristic analysis, and area under the curve values were determined. Multinomial logistic regression analysis was performed to determine independent risk factors for severity of coronary heart disease (age, sex, diabetes mellitus [DM], hypertension, hyperlipidemia, smoking, and MDRD levels). All variables with $p<0.25$ in univariate analysis were included in multivariate analysis. Wald test ("Wald" column) was used to determine statistical significance for each independent variable. The extent to which the dependent variable could be explained by independent variables was assessed by Nagelkerke R2. Hosmer-Lemeshow test was used to determine goodness-of-fit of the logistic regression model. Con-

tinuous non-normally distributed variables were presented as median values and an interquartile range (25th and 75th percentiles). Categorical variables were defined as percentages. All analyses were stratified by severity of CHD. A p value less than 0.05 was considered statistically significant.

## RESULTS

Median age of the study population was 60 years (52–68), and 61.3% of participants were male. Baseline characteristics and biochemical examination data are shown in Table 1. Of the 918 patients, 54.7% had significant CHD, 34.3% had DM, 66.1% had hypertension, 54.6% had hyperlipidemia, and 45.9% were current smokers. Median SYNTAX scores were 9.00 (6.00–12.00), 24.00 (23.00–27.00), and 37.00 (33.50–40.00) in groups I, II, and III, respectively. Higher SYNTAX scores were calculated in men than in women (8.00 [0.00–23.00] and 0.00 [0.00–9.00], respectively; p<0.001). Patients who were diabetic, hypertensive, hyperlipidemic, and smokers had more severe CHD than the controls (p<0.001, in all groups). According to the SYNTAX score, 416 patients (45.3%) had normal coronary arteries or non-significant CHD (SYNTAX score: 0, controls); 267 (29.1%) had mild CHD (SYNTAX score: 1–22, group I); 129 (14.1%) had moderate CHD (SYNTAX score: 23–32, group II); and 106 (11.5%) had severe CHD (SYNTAX score ≥33, group III).

Median eGFR (mL/min/1.73 $m^2$) values were 99.00 (83.00–116.00) in the control group; 85.00 (73.00–101.00) in group I; 87.00 (73.25–101.75) in group II; and 81.00 (65.00–101.00) in group III (Figure 1). According to Spearman's rank correlation analysis, a negative correlation found between eGFR and SYNTAX score was statistically significant (p<0.001, r=-0.268; p<0.001, r=-0.217 in men; p=0.001, r=-0.375 in women). Otherwise, a positive correlation was found between serum creatinine levels and SYNTAX score (p<0.001, r=0.309; p<0.001, r=0.158 in men; p<0.001, r=0.314 in women). In addition, a statistically significant relationship between severity of CHD and eGFR was found (p<0.001; Table 1). Similarly, a statistically significant relationship was found between severity of CHD groups and stage of renal function (p<0.001). A statistically significant reverse correlation between eGFR and age was also found (p<0.001, r=-0.471; Figure 2). In diabetic, hypertensive, and hyperlipidemic patients, eGFR was calculated lower (p=0.001, p<0.001, and p=0.005, respectively). After adjustment according to traditional risk factors including age, DM, hypertension, hyperlipidemia, and smoking status, the correlation between eGFR and SYNTAX score maintained its significance (p<0.001, r=-0.142).

A positive correlation was also found between high-density lipoprotein cholesterol levels and eGFR (p=0.010, r=0.088). A significant inverse correlation was determined between SYNTAX score and high-

**Table 1. Baseline characteristics for the severity of coronary heart disease**

| (N) | Controls (416) | Group I (267) | Group II (129) | Group III (106) | *p* |
|---|---|---|---|---|---|
| Age (year) | 56.00 (48.00–65.00)[a,b,c] | 62.00 (55.00–69.00)[a,d] | 63.00 (56.25–70.00)[b] | 67.50 (59.75–76.00)[c,d] | <0.001*** |
| Gender-n (M/F) | 195/221[a,b,c] | 189/78[a,e] | 105/24[b,e,f] | 74/32[c,f] | <0.001*** |
| Diabetes Mellitus, n (%) | 98 (23.5)[a,b,c] | 103 (38.6)[a,d] | 61 (47.3)[b] | 53 (50)[c,d] | <0.001*** |
| Hypertension, n (%) | 238 (57.2)[a,b,c] | 192 (71.9)[a] | 97 (75.2)[b] | 80 (75.5)[c] | <0.001*** |
| Hyperlipidemia, n (%) | 194 (46.6)[a,b,c] | 160 (59.9)[a] | 77 (59.7)[b] | 70 (66.0)[c] | <0.001*** |
| Smoking-n (%) | 172 (41.3)[a,b] | 142 (53.2)[a,d] | 70 (54.3)[b,f] | 37 (34.9)[d,f] | <0.001*** |
| Creatinine (mg/dL) | 0.72 (0.61–0.88)[a,b,c] | 0.86 (0.73–1.00)[a] | 0.89 (0.77–1.04)[b] | 0.90 (0.77–1.09)[c] | <0.001*** |
| eGFR (mL/min/1.73 $m^2$) | 99.00 (83.00–116.00)[a,b,c] | 85.00 (73.00–101.00)[a] | 87.00 (73.25–101.75)[b] | 81.00 (65.00–101.00)[c] | <0.001*** |
| LDL-C (mg/dL) | 128.97 (101.00–151.00)[a,b] | 118.00 (93.00–150.00)[a] | 113.27 (86.00–140.00)[b] | 120.63 (94.63–145.42) | 0.002** |
| Triglyceride (mg/dL) | 133.23 (92.06–183.00) | 142.00 (101.00–212.74) | 145.00 (100.00–214.30) | 129.00 (89.57–197.75) | 0.051 |
| TC/HDL-C | 4.42 (3.50–5.47)[a,c] | 4.69 (3.78–5.87)[a] | 4.83 (3.60–5.67) | 4.95 (3.74–6.46)[c] | 0.010* |
| FBG (mg/dL) | 96.26 (89.99–108.00)[a,b,c] | 99.00 (91.36–117.74)[a,d] | 103.00 (93.49–124.79)[b] | 108.00 (95.27–144.50)[c,d] | <0.001*** |
| Hemoglobin (g/dL) | 13.90 (12.70–14.90)[a,b] | 14.40 (13.00–15.15)[a,d] | 14.20 (13.20–15.20)[b,f] | 13.60 (12.20–14.60)[d,f] | <0.001*** |

Severity of CHD was determined by SYNTAX Score. C: Controls; CHD: Coronary heart disease; eGFR: Estimated glomerular filtration rate; M: Male; F: Female; FBG: Fasting blood glucose; G: Group; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol. Conover-Inman test was performed for binary comparisons among the groups and p value was set at 0.05. Significant differences were found between; a: C vs GI (p<0.05); b: C vs GII (p<0.05); c: C vs GIII (p<0.05); d: GI vs GIII, (p<0.05); e: GI vs GII, (p<0.05); f: GII vs GIII (p<0.05).

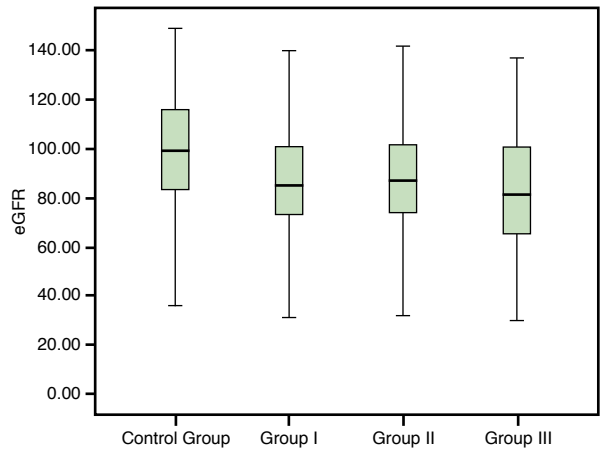


**Figure 1.** Relationship between severity and complexity of coronary heart disease and creatinine clearance according to SYNTAX score. eGFR (mL/min/1.73 $m^2$) was calculated according to Modification of Diet in Renal Disease (MDRD) formula. eGFR: estimated glomerular filtration rate. Values shown as median ($25^{th}$–$75^{th}$ percentiles) in eGFR. Control group: 99.0 (83.00–116.00), group I: 85.00 (73.00–101.00), group II: 87.00 (73.25–101.75), group III: 81.00 (65.00–101.00).

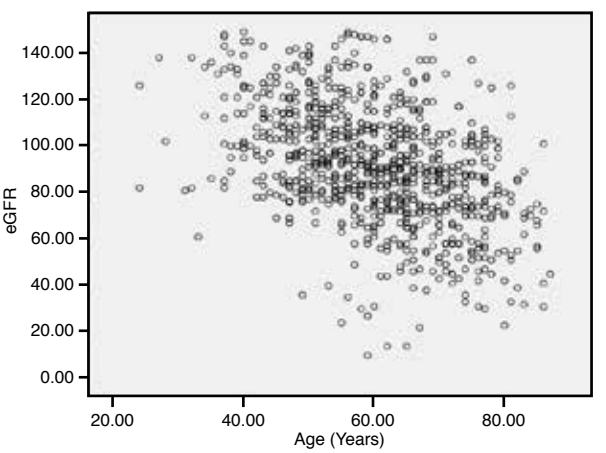


**Figure 2.** Correlation between age and eGFR. eGFR (mL/min/1.73 $m^2$) was calculated according to Modification of Diet in Renal Disease (MDRD) formula. eGFR: Estimated glomerular filtration rate (p<0.001, r=-0.471).

density lipoprotein cholesterol levels (p<0.001, r=-0.217). In multinomial logistic regression analysis, age, sex, DM, hypertension, hyperlipidemia, smoking, and MDRD were covariates. While eGFR (calculated according to MDRD formula) was found to be an independent predictor of severity of CHD; age, sex, DM, hyperlipidemia, and smoking were also found to affect the severity of CHD (Table 2). Cutoff

**Table 2. Multinomial logistic regression analysis for severity of coronary heart disease**

| | Multivariate analysis | | | |
|---|---|---|---|---|
| | Wald | OR | %95 CI | *p* |
| Group I | | | | |
| Age | 9.296 | 1.029 | 1.010–1.048 | 0.002 |
| Sex | 37.817 | 3.297 | 2.254–4.823 | <0.001 |
| eGFR | 21.815 | 0.981 | 0.973–0.989 | <0.001 |
| DM | 5.887 | 1.612 | 1.096–2.370 | 0.015 |
| HT | 3.811 | 1.467 | 0.998–2.155 | 0.051 |
| HL | 5.709 | 1.547 | 1.082–2.214 | 0.017 |
| Smoking | 9.025 | 1.755 | 1.216–2.534 | 0.003 |
| Group II | | | | |
| Age | 15.923 | 1.049 | 1.025–1.074 | <0.001 |
| Sex | 45.428 | 6.363 | 3.715–10.899 | <0.001 |
| eGFR | 9.895 | 0.984 | 0.974–0.994 | 0.002 |
| DM | 10.526 | 2.198 | 1.366–3.538 | 0.001 |
| HT | 4.356 | 1.725 | 1.034–2.878 | 0.037 |
| HL | 0.811 | 1.235 | 0.780–1.957 | 0.368 |
| Smoking | 4.797 | 1.684 | 1.056–2.685 | 0.029 |
| Group III | | | | |
| Age | 36.484 | 1.086 | 1.057–1.115 | <0.001 |
| Sex | 30.053 | 4.492 | 2.625–7.686 | <0.001 |
| eGFR | 7.696 | 0.985 | 0.974–0.995 | 0.006 |
| DM | 9.111 | 2.188 | 1.316–3.639 | 0.003 |
| HT | 0.422 | 1.202 | 0.690–2.095 | 0.516 |
| HL | 6.473 | 1.954 | 1.166–3.275 | 0.011 |
| Smoking | 0.043 | 0.946 | 0.559–1.600 | 0.835 |

Severity of CHD was determined by SYNTAX score (controls: SYNTAX score: 0; group I: SYNTAX score: 1–22; group II: SYNTAX score: 23–32; group III: SYNTAX score ≥33). CI: Confidence interval; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; HT: Hypertension; HL: Hyperlipidemia; OR: Odds ratio. *OR is statistically significant (CI does not include 1). Multinomial logistic regression, Nagelkerke $R^2$=0.290 (Hosmer and Lemeshow p>0.05). Controls were reference category.

value of eGFR for predicting significant CHD (SYNTAX score ≥1) was determined as 91.5 mL/min/1.73 $m^2$ (p<0.001, area under the curve: 0.662, sensitivity: 61.3%, specificity: 61.8%, positive predicted value: 57.2%, and negative predicted value: 66.0%; Figure 3). Median eGFR values (mL/min/1.73 $m^2$) were 96.00 (81.00–114.00), 86.00 (72.75–102.25), and 77.00 (57.00–93.00) in medical therapy, percutaneous coronary intervention (PCI), and coronary artery bypass graft operation groups, respectively (p<0.001 in all comparisons).

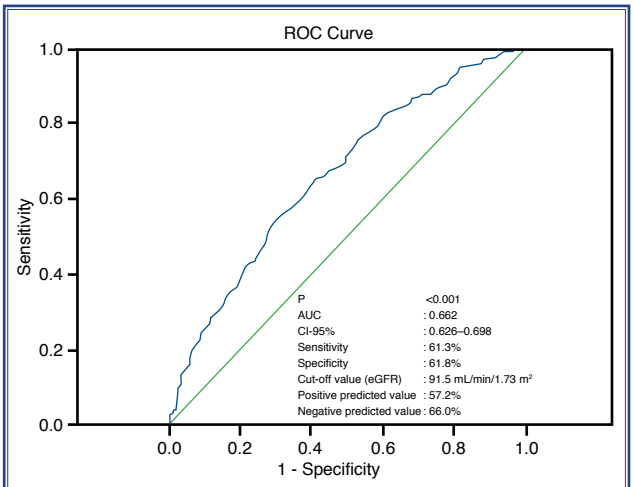


**Figure 3.** Cutoff value of eGFR for predicting significant CHD (ROC curve for SYNTAX score ≥1). AUC: Area under the curve; CHD: Coronary heart disease; eGFR: Estimated glomerular filtration rate; ROC: Receiver operating characteristic.

## DISCUSSION

Even mildly reduced kidney function is significantly associated with CHD severity, independent of other traditional CHD risk factors. CKD is associated with accelerated cardiovascular disease risk. Data from large prospective studies supports that cardiovascular diseases remain the most common cause of morbidity and mortality in patients with CKD.[6] It has been reported that there is an additive contribution of impaired renal function to vascular stiffness, even in patients with moderately severe CHD.[7] Inflammation and oxidative stress are key mechanisms in the development of vascular damage in atherosclerotic CHD.[8] Increased vascular stiffness in patients with renal impairment, however, has also been attributed to inflammation, oxidative stress, and renal arterial calcification.[9,10] Otherwise, besides traditional risk factors, including DM, hypertension, hyperlipidemia, and advanced age, novel risk factors such as endothelial dysfunction, hyperphosphatemia, and hyperparathyroidism are highly prevalent and seem to play a more important role in vascular disease in CKD and ESRD patients, compared with healthy subjects.[11,12] Prothrombotic factors (increased fibrinogen, decreased plasminogen activator inhibitor, and tissue plasminogen activator) and hyperhomocysteinemia are the other causes and the mechanisms of why coronary atherosclerotic lesions are more common and severe in patients with CKD.[13,14] However, it is unclear if impairment of renal function leads to acceleration of these mechanisms in patients with atherosclerotic CHD. Previously mild to moderate renal insufficiency has also been shown to be associated with adverse outcome among patients with acute coronary syndrome.[15–17] Renal dysfunction has proven to be an important determinant of mortality and morbidity in the follow-up of patients who have undergone coronary artery bypass grafting operation or PCI, as well as in the follow-up of those who have suffered from acute coronary syndrome.[18] Some studies have shown an association between renal function and stable CHD. Goodman et al. reported that CHD is common in young adult patients with ESRD.[19] Gradaus et al. have shown that a more rapid progression of atherosclerotic CHD in patients with ESRD is present when compared to patients with normal renal function.[20] Likewise, Henry et al. demonstrated that mild to moderate loss of renal function is strongly associated with an increased risk of cardiovascular mortality.[21] It was recently reported that SYNTAX score was inversely associated with eGFR.[22]

Consistent with the literature, in patients with stable CHD, a lower eGFR estimated by MDRD formula was independently associated with higher SYNTAX score in the present study. Although the correlation we have found between eGFR and SYNTAX score is not strong, its independence from conventional cardiovascular risk factors such as DM, hypertension, hyperlipidemia, smoking, and advanced age is important. Therefore, clinicians should pay more attention to this group of patients with low eGFR. Early stages of renal dysfunction may be the only marker of CHD severity. Alternately, even mild or moderate renal dysfunction may be a pathogenic contributor to the progression of CHD. Therefore, eGFR measured by MDRD formula is an important, simple, effortless, and cost-effective test that should be used more extensively to predict severity of CHD. In addition, to the best of our knowledge, this is the first study to demonstrate that decreased eGFR is associated with treatment modality after coronary angiography. Accordingly, decreased eGFR was often associated with choice of PCI and coronary artery bypass grafting surgery, as patients who underwent invasive treatment procedures had more severe and complex CHD, and further decreased eGFR than the controls.

Our study had certain limitations. First, patients did not undergo intravascular ultrasonography to assess coronary atherosclerotic plaque burden. Secondly, serum creatinine and eGFR measured by MDRD formula were used to classify renal function. Although these methods may be less accurate than measurement of creatinine clearance, they represent measures that are most commonly used in routine clinical practice. Another limitation was the lack of data on albuminuria, which may contribute to cardiovascular effects of renal dysfunction. Despite these limitations, our study investigated the association between renal function, angiographic severity, and complexity of CHD with a large cohort that underwent quantitative coronary angiography and rigorous analysis of CHD risk factors.

Our results demonstrate that decreased eGFR values are associated with significant angiographic CHD evaluated by SYNTAX score in stable patients. This association is independent of traditional CHD risk factors. Regarding the relationship between severity of CHD and eGFR values, this biochemical test can be used to determine cardiovascular disease burden besides other risk factors during routine clinical practice. Future studies are needed to evaluate the pathophysiological mechanism of this finding and the long-term predictive value of eGFR for cardiovascular events in stable individuals.

***Conflict-of-interest issues regarding the authorship or article: None declared***

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*Keywords:* Coronary artery disease; glomerular filtration rate; kidney function; SYNTAX score.

*Anahtar sözcükler:* Koroner arter hastalığı; glomerül filtrasyon hızı; böbrek fonksiyonu; SYNTAX skoru.