

The Effects Of Smoking On The Relationship Between Estimated Glomerular Filtration Rate And The Severity Of Coronary Artery Disease Based On Syntax Score

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Abstract- Background: Chronic kidney disease (CKD) is an independent risk factor and caused high morbidity and mortality for coronary artery disease (CAD). Several scoring systems can be used in assessing the severity of CAD, one of which is using the SYNTAX score (SXscore). Smoking is one of the risk factors for the progression of CAD and CKD. Several observational studies have under-reported the smoking factor influencing the relationship between eGFR and SXscore.

Methods: This research is an observational study with a cross-sectional approach conducted at the Wahidin Sudirohusodo Hospital Makassar from July-August 2020. This study involved 62 CAD and CKD patients undergoing angiography. The estimated glomerular filtration rate was based on chronic kidney disease epidemiology collaboration (CKD-EPI).

Coronary angiography results were converted to SXscore and smoking grade based on the Brinkman index.

Results: This study involved 62 CAD and CKD patients male (71%), aged ≥ 55 years (77.4%), hypertension (71%), diabetes (35.5%), smoking (50%), eGFR G3a & G3b (53.9%) and SXscore medium-high (50%). The results showed that lower eGFR could increase the SXscore ($p < 0.001$), especially in smoking subjects ($p < 0.001$). Multivariate analysis showed that gender was the most significant factor contributing to the relationship between eGFR and SXscore

Conclusion : The lower eGFR could increase the SXscore, where this correlation was more significant in smoking patients. Multivariate analysis showed that gender was the most significant factor contributing to the relationship between eGFR and SXscore.

Keywords: Chronic Kidney Disease, Coronary Artery Disease, SYNTAX Score, Smoking

1. INTRODUCTION

Chronic kidney disease (CKD) is a condition of damage to the kidneys that lasts \geq three months and gives effect for health. Kidney damage here means one or more indicators of kidney damage or a decrease in estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m².(1,2) Some causes of CKD include diabetic kidney disease (52%), hypertensive kidney disease (24%), primary glomerulopathy (6%), obstructive nephropathy (4%), chronic pyelonephritis (3%), uric acid nephropathy (1%), polycystic kidney (1%), lupus nephropathy (1%), and others (8%).(3)

Chronic kidney disease stage is divided into five, normal renal function grade 1 eGFR ≥ 90 ml/min/ 1.73 m², mild renal dysfunction grade 2 eGFR 60-89 ml/min/1.73 m², moderate renal dysfunction grade 3a eGFR 45-59 ml/min/1.73 m², grade 3b eGFR 30-44 ml/min/ 1.73 m², severe renal dysfunction grade 4 eGFR 15-29 ml/min/1.73 m² and kidney failure grade 5 eGFR < 15 mL/min/1.73 m² or undergoing kidney replacement therapy.(4)

Chronic kidney disease is a significant health problem due to its increasing prevalence and high morbidity and mortality mainly caused by cardiovascular disease, in this case, heart failure and coronary artery disease (CAD). Chronic kidney disease is an independent risk factor for CAD. Coronary artery disease is a major cause of morbidity and mortality in CKD patients. The clinical presentation that is not typical of CAD is the cause of the delay in diagnosis and therapy in CKD patients, bringing about the outcome of CAD patients with worse CKD than non-CKD patients.(5)

The severity of CAD can be assessed based not only on the number of coronary vessels involved, but also on the lesion location, and its effect on blood flow, degree of stenosis, lesion classification, vessel diameter and calcification. Several scoring systems can be used in assessing the severity of CAD through an angiographic examination, including using the SYNTAX Score (SXscore).(6)

Smoking is a risk factor for cardiovascular disease and CKD. The mechanisms underlying smoking-induced kidney damage are influenced by several factors. First, susceptible genes or renal polymorphisms play a role in influencing the nephrotoxic effect of smoking. Second, there are more than 4000 chemicals in the form of particles and gases found in cigarette smoke causing nephrotoxic effects. Several studies still state that there is no independent relationship between smoking and CKD.(7–9)

Based on literary study, the relationship between eGFR and SXscore is rarely evaluated and thus we conducted this research.

2. METHOD

2.1 Research Subjects

This study was an observational study with a cross-sectional approach conducted in the Dr. Wahidin Sudirohusodo Hospital Makassar since July-August 2020. The variables assessed were subjects with a decrease in eGFR, where the degree of CKD stage based on chronic kidney disease epidemiology collaboration (CKD-EPI), age, gender, history of hypertension (HT), diabetes mellitus (DM), the smoking status based on the Brinkman index, and the severity of CAD based on coronary angiography converted to a SXscore.

2.2 Inclusion and Exclusion Criteria

Coronary artery disease subjects who experienced CKD and underwent coronary angiography and were willing to participate in the research and sign a letter of approval. The exclusion criteria for subjects were those suffering from valvular heart disease, congenital heart disease, and severe congestive heart disease.

2.3 Data Collection

Data were collected by examining the history of the disease, complete blood chemistry, and the results of coronary angiography converted to a SXscore based on the patient's medical history.

2.4 Diagnosis Criteria

Chronic kidney disease based on kidney disease: improving global outcomes (KDIGO), namely structural or functional damage to the kidneys that lasts \geq three months and a decrease in eGFR < 60 ml/min/1.73m². The estimated glomerular filtration rate was calculated using the formula CKD-EPI with interpretation of G1: eGFR ≥ 90 (normal); G2: eGFR 60-89 (mild); G3a: eGFR 45-59 (mild-moderate); G3b: eGFR 30-44 (moderate-severe); G4: eGFR 15-29 (severe); G5: eGFR < 15 (kidney failure). Coronary artery disease is a condition of stiffness or narrowing of the coronary arteries where the abnormality can be found on electrocardiography and coronary angiography.

The SYNTAX score is a comprehensive tool for assessing coronary angiography results that can determine the complexity of CAD based on the number and characteristics of the coronary lesions involved. The SYNTAX score was calculated based on using the SYNTAX calculator from www.SYNTAXscore.com with interpretation: ≤ 18 (low); 19-26 (moderate); ≥ 27 (high).

Measurement of smoking degree based on the period of smoking history and the number of cigarettes smoked per day that can be determined using the Brinkman index with the following interpretations: 0-200 (mild); 201-600 (moderate); ≥ 601 (severe).

2.5 Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22. The statistical analysis carried out was descriptive statistical calculations and frequency distribution as well as Pearson's Correlation statistical tests, the Chi Square test, and multiple logistic regression (Backward method). The statistical test was significant if the p-value was < 0.05. The risk analysis used Odds Ratio.

2.8 Ethical Permission

This research has fulfilled the ethical requirement from the Commission of Biomedical Research on Human of Medical Faculty in Universitas Hasanuddin with the number of 371/UN4.6.4.5.31/PP36/2020.

3. RESULTS

The study involved 62 patients consisting of 44 male (71%) and 18 female (29%). Fourteen patients aged < 55 years old (22.6%) and 48 were ≥ 55 years old (77.4%). In the blood pressure category, 44 patients (71%) had HT and 18 (29%) of them were non-HT.

Based on the DM category, 22 patients (35.5%) were with DM and 40 (64.5%) were without DM. In the smoking history category, the non-smoking patients were 50%. Meanwhile, the smoking- patients were determined using the Brinkman index and the results were four (6.5%), seventeen (27.4%) and ten (16,1%) patients for light, moderate, and severe categories, respectively.

Based on eGFR category, there were 28 (45.2%), 28 (45.2%) and 6 (9.7%) patients for G2, G3a, and G3b grades, respectively. The SYNTAX score category obtained 20 (32.3%), 12 (19.4%), and 30 (48,4%) patients for the low, moderate, and high categories (Table 1).

Table 1. Categories of research variables (n = 62)

Variable		n	%
Gender	Male	44	71.0
	Female	18	29.0
Age	<55 years old	14	22.6
	≥55 years old	48	77.4
Hypertension	No	18	29.0
	Yes	44	71.0
DM	No	40	64.5
	Yes	22	35.5
Smoking	No	31	50.0
	Mild	4	6.5
	Moderate	17	27.4
	Severe	10	16.1
eGFR	G2	28	45.2
	G3a	28	45.2
	G3b	6	9.7
SXscore	Low	20	32.3
	Moderate	12	19.4
	High	30	48.4

The estimated glomerular filtration rate and SXscore in Table 2 shows a significant relationship between eGFR and SXscore, where the percentage of low and moderate SXscore is higher in eGFR G2 while the highest percentage of SXscore is in G3b ($p < 0.001$). The results of the significant negative correlation test between the eGFR value and SXscore ($p < 0.001$) showed the lower eGFR could increase the SXscore.

Table 2. The Relationship between eGFR and SXscore

eGFR			SXscore			Total
			Low	Moderate	High	
	G2	n	19	7	2	28
		%	67.9%	25.0%	7.1%	100.0%
	G3a	n	1	5	22	28
		%	3.6%	17.9%	78.6%	100.0%
	G3b	n	0	0	6	6
		%	0.0%	0.0%	100.0%	100.0%
Total		n	20	12	30	62
		%	32.3%	19.4%	48.4%	100.0%

$R = 0.782$ ($p < 0.001$)

The role of the smoking factor on the relationship between eGFR and SXscore in table 3 shows a significant relationship between eGFR and SXscore, especially for those who smoked because they had the greatest R-value coefficient ($p < 0.001$).

Table 3. The Relationship eGFR between SXscore based on Smoking Status

Smoking	eGFR		SXscore			Total
			Low	Moderate	High	
No ¹⁾	G2	n	14	1	0	15
		%	93.3%	6.7%	0.0%	100.0%
	G3a	n	1	3	9	13
		%	7.7%	23.1%	69.2%	100.0%
	G3b	n	0	0	3	3
		%	0.0%	0.0%	100.0%	100.0%
Yes ²⁾	G2	n	5	6	2	13
		%	38.5%	46.2%	15.4%	100.0%
	G3a	n	0	2	13	15
		%	0.0%	13.3%	86.7%	100.0%
	G3b	n	0	0	3	3
		%	0.0%	0.0%	100.0%	100.0%

¹⁾ $R = 0.773$ ($p < 0.001$) ²⁾ $R = 0.832$ ($p < 0.001$)

Notes: Smoking status was only divided into non-smoking and smoking since the mild smokers were only four people).

Multivariate analysis in this study aimed to assess confounding variables having a significant role in the relationship between eGFR and SXscore. Based on the 5-step analysis, two variables were not excluded, namely eGFR and gender. This case shows that gender was the most significant factor contributing to the relationship between eGFR and SXscore. The analysis results are shown in Table 4.

Variables	Unstandardized Coefficients		T	p
	B	Std. Error		
eGFR	-0.599	0.093	-6.409	0.000
Gender	-6.750	2.841	-2.376	0.021
Age	-0.253	0.160	-1.579	0.120
Hypertension	3.809	2.573	1.480	0.144
DM	4.589	2.400	1.912	0.061
Smoking	1.886	1.153	1.636	0.107
eGFR	-0.622	0.093	-6.685	0.000
Gender	-6.714	2.871	-2.338	0.023
Age	-0.229	0.161	-1.422	0.160
DM	3.553	2.320	1.531	0.131
Smoking	1.377	1.112	1.238	0.221
eGFR	-0.630	0.093	-6.750	0.000
Gender	-8.657	2.416	-3.583	0.001
Age	-0.212	0.161	-1.317	0.193
DM	3.006	2.289	1.313	0.194
eGFR	-0.655	0.092	-7.124	0.000
Gender	-8.567	2.430	-3.525	0.001
Age	-0.227	0.162	-1.405	0.165
eGFR	-0.610	0.087	-7.015	0.000
Gender	-7.835	2.393	-3.274	0.002

The estimated glomerular filtration rate and SXscore were analyzed based on Table 5 to assess the gender relationship. The analysis results concluded that in male, the mean SXscore was significantly higher in G3a and G3b (32.9 and 32.7) than in G2 (19.2) ($p < 0.001$). In female, the highest mean SYNTAX was in G3b (36.8), then G3a (26.5), and the lowest mean SYNTAX was in G2 (8.6) ($p < 0.001$).

Gender	EGFR	n	Mean	SD	P
Male	G2	19	19.2	8.8	
	G3a	22	32.9	7.8	<0.001
	G3b	3	32.7	6.4	
Female	G2	9	8.6	3.4	
	G3a	6	26.5	10.2	<0.001
	G3b	3	36.8	10.7	

4. DISCUSSION

This study found that most patients studied were 44 male (71%) and 18 female (29%). This result is in line with the research of Ucar, *et al.* They revealed that CAD subjects who had CKD were more in male (60%) than female (40%).(6) The study conducted by Yan, *et al.* involved 2262 CAD subjects with CKD and resulted in more male (70%) than female (30%).(10)

This study found patients aged < 55 years old (22.6%) and aged ≥ 55 years old (77.4%). Research by Na, *et al.* involved 3637 subjects and revealed that CAD patients with undergoing angiography were 70% aged ≥ 55 years old and 30% under 55 years old.(11)

Based on blood pressure category, 44 (71%) had HT and 18 (29%) were non-HT patients. This study is in line with Cho, *et al.* that involved 4297 CAD subjects undergoing coronary angiography and found that the subjects were 80% HT and 20% non-HT.(12) Based on the DM category, there were 22 (35.5%) with DM and 40 patients without DM (64.5%). This study is not consistent with Wright *et al.* who studied 3106 patients with CAD and CKD found that 30% was DM and 60% was non-DM patients.(13) In the smoking history category, 50% of the were non-smoking and the smoking patients were categorized using the Brinkman index. The categorization resulted in four (6.5%) were mild, 17 (27.4%) were moderate, and ten patients (16.1%) were severe. Another study conducted by Hachinohe, *et al.* (2011) involved 5185 subjects experiencing CAD and CKD found 40% were smoking and 60% were non-smoking patients.(14)

Based on kidney function category, 28 (45.2%), 28 (45.2%), and six patients (42.5%) with eGFR G2, G3a, and G3b. This study is in line with the research carried out by Cho, *et al.* (2009) that involved 4297 CAD and CKD subjects undergoing angiography and found that subjects with eGFR G1 and G2 grades were 45% as well as G3a and G3b grades were 55%.(12) The SYNTAX score category obtained 20 (32.3%), 12 (19.4%), and 30 patients (48.4%) for low, moderate, and high categories, respectively. The study of Yan *et al.* (2011) involved 2262 CAD patients undergoing coronary angiography and found that patients with a low, moderate, and high SYNTAX scores were 35%, 33%, and 32%, respectively.(10)

This study showed a significant relationship between eGFR and SXscore, where the percentage of low and moderate SYNTAX was higher in the G2 group while the highest percentage of SXscore was in the G3b group ($p < 0.001$). The results of the correlation test revealed that the eGFR value and the SXscore were significantly negative ($p < 0.001$), where the lower eGFR could increase the SXscore. This study is in line with the research of Yan, *et al.* (2011) that involved 2262 CAD subjects undergoing coronary angiography and found that the lower eGFR could increase the SXscore.(10)

A decrease in eGFR will increase the risk of developing coronary complex lesions progressively as indicated by an increase in the SXscore. In CKD patients, there are several additional factors, such as endothelial dysfunction, increased oxidative stress, high inflammatory process, decreased nitric oxide, platelet mineral bone dysfunction (hyperphosphatemia, hyperparathyroidism, blood vessel calcification), sympathetic hyperactivation, anemia, volume overload, which plays a significant role in the progression of vascular disease in CKD patients.(15–17) Another study by Coskun, *et al.* (2011) showed that CKD patients had more coronary artery calcifications which could increase the SXscore and the degree of CAD severity.(18) The SYNTAX score used in coronary angiography can show the location of the

lesion anatomically, the number of lesions, and the characteristics of the coronary artery lesions, to explain the severity of CAD.(5)

The role of the smoking factor on the relationship between eGFR and SXscore in this study indicated that smoking played a significant role in the significant negative relationship between eGFR and SXscore. The study conducted by Ucar *et al.* found that smoking history did not significantly affect the relationship between eGFR and SXscore.(6) Staplin *et al.* conducted a study on 1243 smokers suffering from CKD and CAD and found that smoking significantly increased mortality and morbidity from cardiovascular events and worsening CKD.(19) The mechanisms underlying smoking-induced kidney damage are influenced by several factors. First, susceptible genes or renal polymorphisms play a role in influencing the nephrotoxic effect of smoking. Second, more than 4000 chemicals in the form of particles and gases found in cigarette smoke that can cause nephrotoxic effects. (8,9) Smoking brings about inflammatory reactions, hypoxia, intrarenal vasoconstriction, hypertension, increased oxidative stress, prothrombotic factors, proinflammatory cytokines that cause intraglomerular hypertension, vascular damage, matrix deposition, glomerulosclerosis, tubular atrophy dysfunction, and widespread atherosclerotic plaque that will increase the worsening CKD and CAD. (20,21)

Multivariate analysis in this study showed that gender was the most significant factor contributing to the negative relationship between eGFR and SXscore. Both male and female gender influenced the significant negative relationship between eGFR and SXscore. Another study by Coskun *et al.* (2011) based on the multivariate analysis found that old age and eGFR were independent predictors of SXscore.(15) Yan, *et al.* (2011) in a multivariate analysis found that DM influencing the relationship between eGFR and SXscore.(10)

4.1 Limitation

Our study limitations was conducted in cross sectional and not all risk factors for CAD were investigated.

5. CONCLUSION

The lower eGFR could increase the SXscore, where this correlation was more significant in smoking patients. Multivariate analysis showed that gender was the most significant factor contributing to the relationship between eGFR and SXscore.

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