

Serum Troponin I Level for Diagnosis of Acute Coronary Syndrome in Patients with Chronic Kidney Disease

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Introduction. Myocardial infarction is a common cause of mortality in patients with chronic kidney disease (CKD). Since troponins I and T levels rise in CKD patients without any myocardial cause, diagnostic value of cardiac troponins is not high in these patients. This study aimed to evaluate the value of troponin I and other cardiac biomarkers to differentiate acute coronary syndrome in CKD patients.

Materials and Methods. In this cross-sectional study, patients with stage 3 to 5 of CKD with typical chest pain were enrolled. Troponins I and T and other biomarkers were measured, and angiography was carried out in these patients. Cardiac biomarkers and other variables were evaluated in patients and compared with angiography results.

Results. Ninety CKD patients with a mean age of 61.67 ± 15.87 years were enrolled. Angiography results were normal in 48.9% of the patients, while it showed single-vessel disease in 14.5%, two-vessel disease in 23.3%, and three-vessel disease in 13.3%. Serum creatinine level, glomerular filtration rate, troponin I level, and creatine kinase level were not significantly different in patients with normal and abnormal angiography findings. The serum troponin I, creatine kinase, and creatine kinase-myocardial bound levels had no significant diagnostic values to differentiate abnormal angiography in CKD patients.

Conclusions. Serum levels of cardiac troponin I and creatine kinase-myocardial bound were not suitable to diagnose ACS in CKD patients (stages 3 to 5); therefore, we suggest using other diagnostic attempts in similar conditions. More evaluation is needed to confirm these findings.

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INTRODUCTION

Chronic kidney disease (CKD) is defined as a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² of body surface for more than 3 months, which may be accompanied with other signs of kidney damage.^{1,2} Acute coronary syndrome (ACS) has a high prevalence in patients with CKD,²⁻⁴ and

myocardial infarction is one of the most important causes of death in CKD patients.^{3,4} Diagnosis of ACS is often difficult. Diagnostic criteria such as clinical demonstrations and electrocardiographic changes in these patients are not definite. Most physicians, based on previous studies, rely on laboratory biomarkers analyses such as troponins I and T.⁵

Troponins I, T, and C are regulatory proteins synthesized in cardioskeletal muscles the serum levels of which increase between 6 to 8 hours after ACS.^{5,6} However in CKD patients, the tendency of using troponins has decreased, because based on recent studies, troponins increase in other conditions such as heart failure.³ Chronic kidney disease also increases the level of troponins I and T.^{3,5,7} About 17% to 75% of CKD patients have increased levels of troponin T and 4% to 21%, troponin I; therefore, diagnostic values of troponin I and troponin T decreased in prediction of cardiac ischemia and they are only the criteria for increasing the risk of future mortality.^{3,8} This study was designed to measure the level of cardiac troponins and other cardiac biomarkers in CKD patients and to determine the value of biomarkers in the diagnosis of ACS.

MATERIALS AND METHODS

This cross-sectional study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences. Ninety samples were calculated a probability of 90% and a *d* of 6% according to previous studies. Patients with stages 3 to 5 of CKD with a typical chest pain and ACS diagnosis, referred to Shahid Labbafinejad Medical Center and Shahid Modarres Hospital, were enrolled. A new-onset retrosternal pain that decreases by sublingual nitroglycerine pearl was considered as typical chest pain. A diagnosis of ACS was made in the presence of rest angina, which was usually more than 20 minutes in duration; new-onset angina that markedly limits physical activity (within 2 months); and increasing angina that was more frequent, longer in duration, or occurred with less exertion than previous angina. An estimated GFR less than 60 mL/min/1.73 m² of body surface for more than 3 months was considered CKD.^{1,2}

Critically ill patients, patients with loss of consciousness, patients who refused to sign an informed consent, those who transferred to another hospital, and patients without angiography were excluded. All of the included patients signed an informed consent. Demographic data, history, and physical examination results were recorded for each patient. Cardiovascular nuclear scan results (if performed before) were recorded as well. Blood urea nitrogen, serum creatinine, and serum cardiac

biomarkers were measured by the same kit and laboratory technique in the central laboratory of each center, at admission. Angiography was performed for all of the enrolled patients and all films were re-evaluated by 1 interventional cardiologist. Standard hydration, N-acetyl cysteine tablet prescription, and discontinuation of diuretics from 24 hours before angiography were considered in nondialysis patients.

The patients were divided into groups by angiography results. They were also categorized based on troponin I levels, into normal (≤ 0.1 ng/mL) and abnormal (> 0.1 ng/mL) subgroups. Data was analyzed using the SPSS software (Statistical Package for the Social Sciences, version 21.0, SPSS Inc, Chicago, Ill, USA). For parametric variables (tested by the 1-sample Kolmogorov-Smirnov test), the independent-sample *t* test was used for comparison of normal and abnormal angiography results and the 1-way analysis of variance to compare angiography subgroups. The Mann-Whitney U and Kruskal-Wallis tests were used for nonparametric variables. The chi-square and Fisher exact tests were used to compare categorical variables in the subgroups. Diagnostic value, cutoff point, specificity, and sensitivity of the biomarkers were measured using the receiver operating characteristic curve methodology. The Pearson correlation test and its nonparametric equivalent (Spearman test) were used to assess the correlation between quantitative variables.

RESULTS

Ninety CKD patients with a mean age of 61.76 ± 18.87 years were evaluated. Fifty-three patients were men and 27 were women. The mean body mass index value was 23.71 ± 2.49 kg/m². Ten patients (11.1%) had a history of kidney transplantation and 7 patients (7.8%) had a history of coronary artery bypass grafting surgery. Thirteen patients (14.5%) had hyperlipidemia, 20 (13.3%) had hypertension, and 16 (17.8%) had diabetes mellitus. The CKD stage was 3 in 50 patients (55.6%), 4 in 31 patients (34.4%), and 5 in 9 patients (10%).

Angiography results were normal in 44 patients (48.9%), single-vessel disease in 13 patients (14.5%), two-vessel disease in 21 patients (23.3%), and three-vessel disease in 12 patients (13.3%). The mean age of the patients with abnormal angiography was significantly higher than those with normal

angiography findings ($P = .001$). The mean creatinine level was 2.58 ± 1.06 mg/dL and the mean GFR was 34.01 ± 12.63 mL/min/1.73 m² of body surface; there was no significant differences in serum creatinine levels, GFR levels, or CKD stages between the patients with normal and abnormal angiography findings or between those with 1 to 3 vessels involved.

The mean troponin I level was 0.95 ± 1.44 ng/mL in those with normal angiography and 1.82 ± 2.96 ng/mL in those with abnormal angiography ($P = .08$). The mean troponin I level was 1.24 ± 2.89 ng/mL in the patients with single-vessel disease, 1.94 ± 2.41 ng/mL in those with two-vessel disease, and 2.24 ± 3.95 ng/mL in those with three-vessel disease ($P = .08$). Twenty patients of those with normal angiography (45.5%) and 27 of those with abnormal angiography (58.7%) had positive results for troponin I ($P = .21$). The mean creatine kinase-myocardial bound (MB) was 19.59 ± 5.47

ng/mL in the normal angiography group and 22.87 ± 10.13 ng/mL in the abnormal angiography group ($P = .33$). There was also no significant difference in the mean creatine kinase-MB level between patients with normal angiography and those with different vessel diseases ($P = .06$; Tables 1 and 2). There was a significant correlation between serum levels of troponin I and creatine kinase-MB ($r = 0.319$, $P = .002$).

Troponin I-positive and troponin I-negative patients had significant differences in serum creatinine level, GFR, creatine kinase, and creatine kinase-MB (Table 3). The receiver operating characteristic curve showed that creatine kinase-MB, troponin I, creatine kinase could not differentiate patients with normal and abnormal angiography results (Figure).

DISCUSSION

According to our results, serum troponin I and

Table 1. Comparison of Patients With Normal and Abnormal Angiography Results

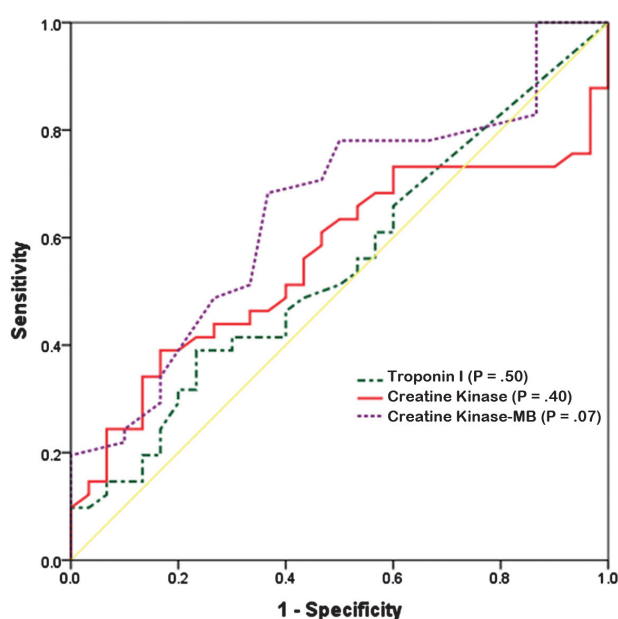
Parameter	Angiography Results		P
	Normal	Abnormal	
Age, y	55.93 ± 17.47	67.33 ± 11.91	.001
Male sex (%)	24 (54.5)	29 (63.0)	> .05
Creatinine, mg/dL	2.635 ± 1.139	2.523 ± 0.994	> .05
Glomerular filtration rate, mL/min/1.73 m ²	35.66 ± 13.86	32.46 ± 11.29	> .05
Chronic kidney disease (%)			
Stage 3	26 (59.1)	24 (52.2)	
Stage 4	12 (27.3)	19 (41.3)	
Stage 5	6 (13.6)	3 (6.5)	> .05
Troponin I, ng/mL	0.95 ± 1.44	1.82 ± 2.96	> .05
Positive troponin I	20 (45.5)	27 (58.7)	> .05
Creatine kinase	159.93 ± 63.61	179.78 ± 88.63	> .05
Creatine kinase-MB	19.59 ± 5.47	22.87 ± 10.13	> .05

Table 2. Comparison of Patients With Normal Angiography Results and Single-Vessel Disease (SVD), 2-Vessel Disease (2VD), and 3-Vessel Disease (3VD)

Parameter	Angiography Results				P
	Normal	SVD	2VD	3VD	
Age, y	55.93 ± 17.47	58.08 ± 14.06	72.81 ± 8.5	67.82 ± 8.22	< .001
Male sex (%)					> .05
Creatinine, mg/dL	2.635 ± 1.139	2.605 ± 1.194	2.598 ± 0.872	2.303 ± 1.018	> .05
Glomerular filtration rate, mL/min/1.73 m ²	35.66 ± 13.86	36.17 ± 12.39	28.61 ± 7.98	35.42 ± 13.83	> .05
Chronic kidney disease (%)					
Stage 3	26 (59.1)	8 (61.5)	9 (42.9)	7 (58.3)	
Stage 4	12 (27.3)	5 (38.5)	11 (52.4)	3 (25)	
Stage 5	6 (13.6)	0	1 (4.8)	2 (16.7)	> .05
Troponin I, ng/mL	0.948 ± 1.44	1.244 ± 2.89	1.94 ± 2.41	2.24 ± 3.95	> .05
Positive troponin I	20 (45.5)	5 (38.5)	16 (76.2)	6 (50.0)	> .05
Creatine kinase	159.93 ± 63.61	160.0 ± 88.16	186.3 ± 79.78	188.08 ± 105.5	> .05
Creatine kinase-MB	19.5 ± 9.56	21.54 ± 10.38	20.38 ± 9.11	28.67 ± 10.06	> .05

Table 3. Comparison of Patients With Negative (≤ 0.1 ng/mL) and Positive (> 0.1 ng/mL) Troponin I

Parameter	Troponin I		P
	Positive	Negative	
Age, y	63.5 \pm 14.7	59.8 \pm 17.0	> .05
Male sex (%)	30 (63.8)	23 (53.5)	> .05
Creatinine, mg/dL	2.77 \pm 1.02	2.36 \pm 1.08	.01
Glomerular filtration rate, mL/min/1.73 m ²	30.9 \pm 11.1	37.5 \pm 13.4	.01
Chronic kidney disease (%)			
Stage 3	22 (46.8)	28 (65.1)	
Stage 4	21 (44.7)	10 (23.3)	
Stage 5	4 (8.5)	5 (11.6)	> .05
Creatine kinase	198.68 \pm 79.36	126.90 \pm 55.90	< .001
Creatine kinase-MB	23.29 \pm 8.85	19.16 \pm 7.20	.02



The receiver operating characteristic curve shows the diagnostic value of troponin I, creatine kinase, and creatine kinase-MB to differentiate normal and abnormal angiography results.

CK-MB levels had no diagnostic value for ACS in CKD patients. Results of this study were different with those published by Flores-Solis and colleagues on the diagnostic values of CK-MB and troponin I⁹; cardiac evaluations of their study were based on history taking, physical examination, and electrocardiography.⁹ In another study population, Flores-Solis and colleagues reported a 70% sensitivity and a 92% specificity for troponin I of more than 0.05 ng/mg in the diagnosis of ACS in CKD patients.¹⁰ They also studied 426 CKD patients with stages 3 to 5 and reported higher troponin I levels in patients of stage 5 than others.¹¹ This study indicated that increased troponin I in CKD patients is not related to ACS occurrence in the

coming 6 months.¹¹

In Kumar and colleagues' study, examining patients without any cardiac symptoms and under hemodialysis, it was stated that a troponin level lower than 0.034 ng/mL was common in these patients. Increased troponin level was related to a history of coronary artery disease, left ventricle hypertrophy, low ejection fraction of left ventricle, and high serum phosphate.¹²

Kalaji and coworkers introduced the best cutoff point of 0.03 ng/mL for troponin T and 0.2 ng/mL for troponin I in hemodialysis patients. In this study, ACS patients were followed for 2 years regarding cardiac accidents and death.¹³ Chen and colleagues considered a troponin I cutoff point of 0.06 ng/mL, and 43.34% of patients without ACS had results for troponin I. In total, 26% of patients in this study had positive findings for troponin T. This study compared positive and negative troponin patients and a relative increase in troponin I with cardiac disorder in non-ACS patients.¹⁴

Zand Parsa and colleagues assessed the association between an increase in troponin T and GFR and creatinine levels and concluded that creatinine level and GFR had no significant association with troponin I and left ventricular ejection fraction, while the results of our study showed the association between creatinine and GFR with troponin.¹⁵ Apple and coworkers reported a 2-year mortality rate of 30% in patients with negative troponin I (less than 0.1 μ g/L) and 59% in those with positive troponin I findings.¹⁶ In this study, patients with end-stage renal disease and non-ACS patients had 80% positive troponin T and 6% positive troponin I.¹⁶ Acharji and colleagues evaluated troponin I in CKD patients and reported that troponin was a suitable factor for myocardial

infarction prognosis in patients with higher levels of troponin, but it was not a suitable factor for myocardial infarction prognosis in patients with lower troponin levels.¹⁷

Ten patients with kidney transplant were investigated by Bozbas and coworkers, and it was confirmed that kidney transplant had no significant effect on troponin and CK-MB levels in CKD patients.¹⁸ Bozbas and coworkers considered creatine-MB with low sensitivity and specificity in ACS diagnosis in all CKD patients, but cardiac creatine-MB had an appropriate diagnostic value in kidney transplant patients. In this study, troponin I had a better diagnostic value than troponin T and creatine kinase-MB in the diagnosis of myocardial infarction.¹⁹

There is a significant association between CKD stage and creatinine level and cardiac troponin.²⁰ Troponin I and troponin T has direct associations with GFR and CKD and this association is more significant for troponin T than troponin I.²¹ An increase in cardiac troponin is related with coronary artery calcification (studied with CT scan).²¹

Korkmaz and colleagues studied patients under hemodialysis and non-ACS patients and showed higher importance of creatine kinase-MB than troponin I in CKD patients.²² In Mutlung and associates' study, troponin I (provided by accurate laboratory methods) was a good marker for diagnosis of atherosclerosis in end-stage renal disease patients and its diagnostic value was higher than creatine kinase-MB.²³ Ahmadi and colleagues evaluated serum levels of troponins I and T in CKD patients without ACS, showing the elevated levels of these troponins in patients without ACS.⁸ Their results was similar to our results in terms of a significant correlation between troponin I with serum creatinine and GFR.⁸

Using other diagnostic criteria is suggested instead of troponin I and creatine kinase-MB for ACS diagnosis in CKD patients, in similar setting. The lack of significant values for troponin I and creatine kinase-MB in the diagnosis of ASC in stages 3 to 5 CKD patients could be because of different laboratory techniques and accuracy in the mentioned laboratory.

It is suggested to perform similar studies with other laboratory kits and cut points. Future studies also can compare kidney patients with and without ACS in two certain groups with higher samples.

Differences in study results with previous studies may be due to confounding effect of serum creatinine and GFR on troponin. This effect is scattered in previous studies but this study observed a significant association between creatinine and GFR with troponin level. Confounding effect of serum creatinine and GFR should be considered on troponin I in future studies. In this study, troponin had a direct association with creatine kinase-MB. Previous studies did not perform angiography, which could be the reason of different views on diagnostic value of troponin and different methods.

CONCLUSIONS

Serum levels of cardiac troponin I and creatine kinase-MB were not suitable to diagnose ACS in CKD patients (stages 3 to 5); therefore, we suggest using other diagnostic attempts in similar conditions. More evaluations are needed to confirm these findings.

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CONFLICT OF INTEREST

None declared.

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