An Analysis of Factors Affecting 90-Day Survival in Patients whose First Presentation of Cardiovascular Disease was an Acute Coronary Event

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ABSTRACT

Background: Acute coronary syndrome (ACS) is a life-threatening manifestation of atherosclerosis. Despite marked improvements in in-hospital outcomes for patients with ACS, short- and long-term outcomes after hospital discharge remain poor. Patients with previous myocardial infarction, multivessel disease, and partial revascularization have higher mortality and morbidity rates following the second ACS event. However, few studies have analyzed the characteristics that influence outcomes in patients with the first ACS event. Several studies have reported associations between poor clinical outcomes in patients with ACS and each of the following factors: sex, advanced age, glomerular filtration rate, bundle branch block on electrocardiography, and left anterior descending (LAD) artery disease as the infarct-related artery.

Objective: To determine which of these factors is associated with poor outcomes (a composite of death, reinfection, or hospitalization for heart failure) within the first 90 days in discharged patients whose first presentation of cardiovascular disease was ACS.

Design : A Retrospective Study.

Setting: Cardiology department, University Hospital Center Zagreb, Croatia.

Methods: Participants comprised 2565 patients with ACS between January 2013 and December 2017.

Results:. Logistic regression analyses revealed the LAD artery as the culprit artery and renal function as important predictors. Moreover, older female patients with the LAD artery as the culprit artery and impaired renal function were a high-risk subgroup.

Conclusion : These findings may aid clinicians in identifying high-risk patients who would most benefit from intensive follow-up and aggressive risk factor reduction and help tailor diagnostic and therapeutic strategies at the individual level.

Keywords: Chronic kidney disease, Myocardial infarction, Outcome, Risk factors, Sex

INTRODUCTION

Acute coronary syndrome (ACS) is a life-threatening manifestation of atherosclerosis[1]. Pathological, imaging, and biological observations have indicated that atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis, form the basic pathophysiological mechanisms of most ACS conditions[2-4]. ACS refers to any group of clinical symptoms compatible with acute myocardial ischemia, including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI)[5]. Over the past decade, the prognosis of patients with ACS has improved due to secondary prevention measures, the implementation of strict guidelines, early revascularization, and antithrombotic therapies. Despite a marked improvement in in-hospital outcomes for patients with ACS, short- and long-term outcomes after hospital discharge remain poor[5,6].

Studies investigating the effect of specific predictors that could be causally associated with poor clinical outcomes are urgently required. Risk stratification is essential in the decision-making process as it can guide secondary prevention measures, therapies, and patient follow-up. Furthermore, individual patient risk assessment can guide appropriate management strategies at hospital discharge.

The following specific factors have been reported to be associated with poor clinical outcomes in patients with ACS: sex[7-12], advanced age, glomerular filtration rate (GFR)[13-18], bundle branch block (BBB) in the electrocardiogram (ECG)[19,20], and left anterior descending (LAD) artery as the infarct-related artery. This study aimed to determine which of these variables are statistically associated with poor outcomes in the first 90 days post-discharge in patients whose first presentation of cardiovascular disease (CVD) was in the form of ACS.

METHODS

Study Design: We conducted a single-center, retrospective study of patients with ACS (STEMI, NSTEMI, and UA) treated at the University Hospital Center Zagreb, Zagreb, Croatia, between January 2013 and December 2017. This study derived data from the Croatian branch of the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC) Registry, which is headquartered

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at the University of Bologna. All patients involved in this study (age > 18 years) provided written informed consent prior to enrollment in the registry. The University Hospital Center Ethics Committee approved this study (approval number 8.1 17/76-2 date/23.05.2012).

Patients: The study population comprised 2565 patients with ACS between January 1, 2013, and December 31, 2017. Inclusion criteria comprised patients with discharge diagnoses of STEMI, NSTEMI, or UA. Exclusion criteria comprised a history of previous myocardial infarction (treated with percutaneous coronary intervention [PCI], fibrinolysis, optimal medical therapy, or coronary artery bypass grafting), known peripheral artery disease, death during the index hospitalization, and lack of follow-up data (mainly because the patient's residence was outside the center's service area).

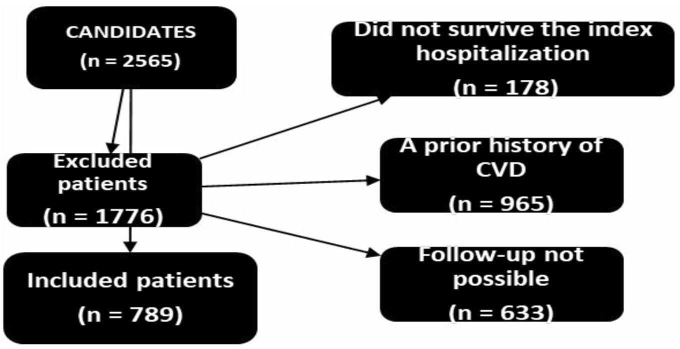

Figure 1: Recruitment and selection of the patient cohort

Initially, the data of 2565 patients were screened retrospectively. All patients not fulfilling the study inclusion criteria or without available follow-up were excluded. Data on symptoms and clinical characteristics were obtained by a cardiologist or cardiology resident within the first 48 h after admission. Medical records were reviewed to extract data regarding relevant clinical and laboratory parameters during hospitalization. The different types of ACS were diagnosed based on the patient's symptoms, biochemical marker levels, and ECG results (using European Society of Cardiology clinical practice guidelines). All patients underwent coronary angiography (ad-hoc PCI) within 72 h of admission.

Statistics: Prior to testing the effects of each predictor on outcomes and mortality, the data distribution was tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests (Table 1). P-values of <0.05 were considered to indicate a normal distribution; accordingly, parametric tests were applied.

Table 1: Tests of normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	Df	Sig.	Statistic	df	Sig.
Agee	.05	704	.001	.99	.704	.003
GFR	.04	704	.009	.98	.704	.000

a.- Lilliefors significance correction

GFR- glomerular filtration rate

Logistic regression analysis was performed to evaluate the association between variables of interest (sex, age group, BBB, GFR, and affected artery) and study endpoints, composite of adverse outcomes (reinfection or hospitalization) and mortality; the 95% confidence interval (CI) is reported. Logistic regression analysis can be performed to estimate the relationship between one non-metric (binary) dependent variable and a group of metric or non-metric independent variables.

Two-sided p-values <0.05 were considered statistically significant. All analyses were performed using SPSS statistical software (version 21.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Table 2 shows the patient characteristics and mortality status at 90 days post-hospital discharge according to the infarcted artery (LAD, right coronary artery [RCA], and left circumflex [LCx] artery).

Table 2: Ninety-day patient status (survived/deceased) according to the reported culprit artery

		Infarction-related artery					
		LAD		RCA		LCx	
		N	%	N	%	N	%
90-day survival	**Dead**	29	8.4%	13	5.5%	8	4.2%
	Alive	316	91.6%	243	94.5%	179	95.8%
	Total	345	100.0%	256	100.0%	187	100.0%

LAD, left anterior descending artery
RCA, right coronary artery
LCx, left circumflex artery

Composite Endpoint: Table 3 shows the results of the logistic regression model analysis for 90-day survival from a composite of adverse outcomes in all patients. Renal function and affected artery were the best predictors of better outcomes. Elevated GFR indicated a 1.86 higher probability of better outcomes, and survival from the composite of adverse events was 0.28 times better in patients with infarctions involving the RCA or LCx artery than in patients with LAD infarction. No other variables were significantly associated with 90-day survival from the composite endpoint.

As LAD infarction was a statistically important predictor of 90-day survival from the composite endpoint, the same logistic regression model was applied to the subgroup of patients with the LAD artery as the culprit artery (Table 4). In older age groups, there was a 0.19 times higher risk of a poor outcome (death, reinfection, or hospitalization for heart failure) than in lower age groups, whereas a poor outcome was 8.139 times more likely to occur in women than in men. Moreover, in this model, the GFR remained a significant predictor of the outcome. Thus, age, sex, and GFR were revealed as the most influential predictors of a poor outcome.

Mortality: Associations between variables of interest and 90-day mortality in the LAD-culprit subgroup were investigated in individual regression analyses.

Age Categories: Table S1 in the Supplementary Material shows differences in 90-day mortality between patient age groups. Survival outcomes were poorest for older patients. Of patients who died in the first 90 days post-hospital discharge, 82.8% (n = 24) were aged ≥66 years, whereas in the 46–66-year age group, only 17.2% (n = 5) died, and no deaths occurred among younger patients. The differences between age groups reached statistical significance (chi-square test: p = 0.001; Table S2 in the Supplementary Material).

Renal Function: Furthermore, patients were divided into five renal function groups, as shown in Table S3 in the Supplementary Material. Patients with a GFR of <15 mL/min/1.73 m^2 had the highest mortality rate (three of five patients) in the first 90 days post-hospital discharge. The lowest mortality rate was found in patients with a GFR of ≥90 mL/min/1.73 m^2, with only one death among 81 patients in the first 90 days post-hospital discharge. The differences between renal function

Table 3: Regression model for 90-day survival and selected variables, including the infarcted artery

		B[1]	S.E.[2]	Wald[3]	df[4]	Sig.[5]	Exp(B)[6]	95% CI	
								Lower	Upper
Step 1[a]	**Age group**	-1.01	.55	3.40	1	.07	.36	.12	1.07
	Sex	.36	.53	.47	1	.50	1.43	.51	4.00
	Ninety-day hospitalization	-20.03	4054.37	.00	1	>.99	.00	.00	.
	Bundle block	-.29	.78	.14	1	.70	.75	.16	3.40
	GFR group	.62	.22	8.03	1	**.005**	1.86	1.21	2.86
	LAD/RCA and LCx	-1.27	.52	6.09	1	**.01**	.28	.10	.77
	Constant	22.02	4054.37	.00	1	>.99	3663806067.13		

a. Variable(s) entered on step 1: age group, sex, rehospitalization, bundle block, GFR group, and LAD/RCA/LCx.

[1]Values of the logistic regression, coefficients of the equation predicting the dependent variable with independent variable
[2]Standard errors associated with coefficients
[3]Wald value of the chi-square test
[4]Degrees of freedom
[5]Values of coefficient significance
[6]Predictor odds ratio
CI, confidence interval
LAD, left anterior descending artery
RCA, right coronary artery
LCx, left circumflex artery
GFR, glomerular filtration rate

Table 4: Regression model for 90-day survival and selected variables in patients with LAD as the culprit artery

		B[1]	S.E.[2]	Wald[3]	df[4]	Sig.[5]	Exp(B)[6]	95% CI	
								Lower	Upper
Step 1[a]	**Age categories**	-1.66	.81	4.24	1	**.04**	.19	.04	.92
	Sex	2.10	.88	5.64	1	**.02**	8.14	1.44	45.96
	Hospitalization 3M	-21.04	5580.14	.00	1	>.99	.00	.00	.
	Bundle block	1.06	1.31	.66	1	.42	2.90	.22	37.81
	GFR categories	1.20	.39	9.39	1	**.002**	3.33	1.54	7.18
	Constant	38.64	11160.29	.00	1	>.99	60507550481083968.00		

a. Variable(s) entered on step 1: age categories, sex, hospitalization, bundle block, GFR categories.

[1]Values of logistic regression, coefficients of the equation predicting the dependent variable with independent variable
[2]Standard errors associated with coefficients
[3]Wald value of the chi-square test
[4]Degrees of freedom
[5]Values of coefficient significance
[6]Predictor odds ratio
CI, confidence interval
GFR, glomerular filtration rate
LAD, left anterior descending artery

groups reached significance (chi-square test: $p < 0.05$; Table S4 in the Supplementary Material), with significantly lower GFR value in deceased patients.

Bundle Branch Block and Sex: Bundle branch block did not significantly predict 90-day mortality (0.50, $p > 0.05$). Additionally, sex was not a significant risk factor for increased 90-day mortality (0.32, $p > 0.05$; Tables S5 and S6 in the Supplementary Material).

DISCUSSION

Using logistic regression analysis, we evaluated the association between select variables of interest, including sex, age group, BBB, GFR, and culprit artery (LAD, RCA, or LCx artery) and poor outcomes within 90-day post-discharge (a composite of death, reinfection, and hospitalization for heart failure). Our findings indicated that only low GFR and LAD infarction were significant predictors of poor outcomes in the total study population. When the same regression model was applied to patients with LAD as the infarcted artery, older age groups had a higher probability of poor outcomes. Additionally, poor outcomes were approximately eight times more likely in women than in men. Furthermore, GFR was negatively associated with survival in these patient groups.

Regarding individual regression analyses, the significant indicators for 90-day outcomes comprised age, rehospitalization, and renal impairment. Among age groups, mortality was poorest in older patients. In the subgroup with LAD as the culprit artery, 82.8% of patients who died in the first 90 days post-hospital discharge were aged ≥66 years, whereas only 17.2% of patients in the 46–66 year age group died during this period, and no deaths occurred among younger patients. Results from the PRAMI trail[21,22] and the APEX trail[23] showed that age was a strong predictor of in-hospital and 90-day mortality. Despite technological modernization and developments in the field of invasive cardiology, as well as the implementation of new guidelines for the treatment and timing of interventions, the present study results indicate that older patients remain at high risk of post-infarction rehospitalization and death in the first 90 days, and that age was an important predictor of 90-day survival in patients with ACS as the first presentation of CVD. Further, patients who died within the first 90 days had at least one rehospitalization. A possible limitation of the present study is that some of the patients may have died outside the hospital; however, the relevant data were not available in our registry.

Diagnosis of ACS in women remains challenging as women are more likely to present with vasospastic disease or atypical symptoms, such as dyspnea. Atypical presentations could be attributed to differences in the anatomy, pathophysiology and clinical manifestations of atherosclerosis in women[8,10]. While men generally have a higher risk of developing atherosclerosis, multiple global registries have consistently shown that women with ACS are at considerably higher risk of adverse outcomes than men[9-12]. However, whether female sex is an independent contributor, or differences in baseline characteristics and comorbidities contributes to their higher risk, remains unclear. Some studies[24,25] have shown that female sex is associated with a considerably higher risk of poorer short-term outcomes. In a 2017 study of patients with STEMI, Venetsanos et al. showed that this sex difference was mainly due to a higher risk of all-cause mortality in women vs. men (5.7% vs. 1.9%, respectively); while sex differences were diminished in a multivariable model, female sex was still found to be associated with higher all-cause mortality[24]. Furthermore, Jakobsen et al. evaluated post-PCI survival in patients and found that composite endpoints of mortality, reinfarction, and stroke at 30 days and at one year for women were 9.1% and 16.0%, respectively, compared with 5.8% and 10.6%, respectively, for men[25]. In a 2013 study conducted in Qatar, the effect of sex as a risk factor for patients with ACS was evaluated; multivariate logistic regression analysis showed that female sex was an independent predictor of in-hospital mortality (odds ratio: 1.51, 95% CI: 1.27–1.79)[26]. In contrast, Cho et al. found that although women had higher rates of major adverse cardiovascular events (MACEs) than men (7.8% vs. 4.7%; p=0.004), female sex was not an independent predictor of MACEs after adjusting for propensity score matching[10]. In the present study, individual regression analysis did not indicate sex as a risk factor for an increased 90-day mortality in patients with ACS without previously diagnosed CVD. However, when the same regression model was used only in patients with LAD as the culprit artery, women were approximately eight times more likely to have an unfavorable outcome (death, reinfection, or hospitalization for heart failure) than men.

Chronic kidney disease remains a global health challenge. Ischemic heart disease is known to be more prevalent in patients with renal dysfunction. Kidney function is a strong risk factor for fatal and nonfatal cardiovascular events, and patients who require long-term renal replacement therapy are at particularly high risk[13-15,27]. Historically, cardiologists have not considered a mildly reduced GFR level as having any prognostic value for survival; however, two recent studies suggested that even mildly decreased kidney function is an independent predictor of long-term mortality in patients with ACS[15-18,28]. Homorodean et al. reported that in patients with STEMI with the left main coronary artery as the culprit vessel who underwent PCI, low eGFR was associated with increased mortality at 1-year follow-up[29]. A 2013 meta-analysis that combined the data of four large, randomized trials (namely, the VALIANT, EPHESUS, OPTIMAAL and CAPRICORN), reported that GFR was strongly and independently associated with poor outcomes in patients with post-myocardial infarction[17]. The present finding of an association between the GFR value and 90-day survival, with higher GFR in survivors, is consistent with that of previous studies. Furthermore, we observed that the GFR value was lower in patients with at least one rehospitalization within the first 90 days post-discharge.

In patients with the LAD artery as the culprit artery, those with a GFR of <15 mL/min/1.73 m^2 had the highest mortality rate (three of five patients) in the first 90 days post-hospital discharge. The lowest mortality rate (1 of 81 patients) was observed in the patient group with a GFR of ≥90 mL/min/1.73 m^2. Higher mortality has been associated with higher grades of kidney disease and less aggressive treatment during the hospital stay. The present findings confirmed that higher mortality is associated with higher grades of kidney disease, which supports the importance of considering the GFR value, particularly in patients with ACS as the first presentation of CVD.

BBB often blurs ischemic ECG changes, and although it is not yet fully understood, BBB has been hypothesized as a risk factor for mortality and clinical outcome after ACS[19,20]. However, in the present study, BBB was not associated with poorer outcomes at 90 days post-discharge (in the total study population and in the subset with LAD as the culprit artery).

CONCLUSION

LAD as the culprit artery and renal function are important predictors of 90-day outcomes in patients whose first presentation of CVD was an ACS event. In particular, we found that older female patients with LAD artery as the culprit artery with impaired renal function were a high-risk subgroup. A more comprehensive follow-up algorithm in patients for whom predictors of adverse clinical outcomes have been found is essential; hence, our findings may lead to improved secondary prevention, both during hospitalization and following discharge.

In conclusion, mandatory individualized risk assessment at hospital discharge is strongly recommended to identify high-risk patients or high-risk subgroups, using the predictors of poor outcome identified in the present study. Diagnostic and therapeutic strategies can then be tailored at the individual level and determine whether closer and more frequent follow-up is necessary for such patients.

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Competing Interest: None

Sponsorship: None

Ethical Approval: The University Hospital Center Ethics Committee approved this study (approval number 8.1 17/76-2).

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REFERENCES

1. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. JAMA 1983;250(13):1757-65.
2. Lee KY, Chang K. Understanding vulnerable plaques: current status and future directions. Korean Circ J 2019;49(12):1115-22

3. Hafiane A. Vulnerable plaque, characteristics, detection, and potential therapies. *J Cardiovasc Dev Dis* 2019;*6(3)*:26.
4. Stefanadis C, Antoniou CK, Tsiachris D, et al. Coronary atherosclerotic vulnerable plaque: current perspectives. J Am Heart Assoc 2017;6(3):e005543.
5. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. Circulation 2018;138(20):237-69.
6. Valley TS, Iwashyna TJ, Cooke C, et al. Intensive care use and mortality among patients with ST elevation myocardial infarction: retrospective cohort study. BMJ. 2019;365:l1927.
7. Lekston A, Tajstra M, Gąsior M, et al. Impact of multivessel coronary disease on one-year clinical outcomes and five-year mortality in patients with ST-elevation myocardial infarction undergoing percutaneous coronary intervention. Kardiol Pol 2011;69(4):336-43.
8. Vakhtangadze T, Singh Tak R, Singh U, et al. Gender differences in atherosclerotic vascular disease: from lipids to clinical outcomes. Front Cardiovasc Med 2021;8:707889.
9. Ghaffari S, Pourafkari L, Tajlil A, et al. Is female gender associated with worse outcome after ST elevation myocardial infarction? Indian Heart J. 2017;69:S28–S33.
10. Cho KI, Shin ES, Ann SH, et al. Gender differences in risk factors and clinical outcomes in young patients with acute myocardial infarction. J Epidemiol Community Health 2016 70(11):1057-64
11. Meyer MR, Bernheim AM, Kurz DJ, et al. Gender differences in patient and system delay for primary percutaneous coronary intervention: current trends in a Swiss ST-segment elevation myocardial infarction population. *Eur Heart J Acute Cardiovasc Care* 2019;8(3):283-90.
12. Stehli J, Martin C, Brennan A, et al. Sex differences persist in time to presentation, revascularization, and mortality in myocardial infarction treated with percutaneous coronary intervention. J Am Heart Assoc 2019;8(10):e012161
13. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *New Engl J Med* 2004;351(13):1296-1305.
14. Bhandari S, Jain P. Management of acute coronary syndrome in chronic kidney disease. J Assoc Physicians India. 2012;60:48-51.
15. Klein EC, Kapoor R, Lewandowski D, et al. Revascularization strategies in patients with chronic kidney disease and acute coronary syndromes. *Curr Cardiol* Rep 2019;21(10):113.
16. Zannad F, Rossignol P. Cardiorenal syndrome revisited. Circulation 2018;138(9):929-44.
17. Campbell NG, Varagunam M, Sawhney V, et al. Mild chronic kidney disease is an independent predictor of long-term mortality after emergency angiography and primary percutaneous intervention in patients with ST-elevation myocardial infarction. Heart 2012; 98(1):42-7.
18. Moukarbel GV, Yu ZF, Dickstein K et al. The impact of kidney function on outcomes following high risk myocardial infarction: findings from 27 610 patients. *Eur J Heart Fail* 2014;16(3):289-99.
19. Fabijanovic D, Planinc I, Jakus N, et al. Bundle branch block increased in hospital mortality in acute coronary syndrome patients. Results of the Croatian ISACS Registry. Cardiol Croat 2017:129(9):690-7.
20. Go AS, Barron HV, Rundle AC et al. Bundle-branch block and in-hospital mortality in acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *Ann Intern Med.* 1998; 129(9):690-7.
21. Stone GW, Marsalese D, Brodie BR, et al. A prospective, randomized evaluation of prophylactic intraaortic balloon counterpulsation in high-risk patients with acute myocardial infarction treated with primary angioplasty. J Am Coll Cardiol 1997;29: 29(7):1459-67.
22. Wharton TP Jr, Grines LL, Turco MA, et al. Primary angioplasty in acute myocardial infarction at hospitals with no surgery on-site (the PAMI-No SOS study) versus transfer to surgical centers for primary angioplasty. J Am Coll Cardiol 2004;43(11):1943-50.
23. Gharacholou SM, Lopes RD, Alexander KP, et al. Age and outcomes in ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: findings from the APEX-AMI trial. Arch Intern Med. 2011;171(6):559-67.
24. Venetsanos D, Sederholm Lawesson S, Alfredsson J, et al. Association between gender and short-term outcome in patients with ST elevation myocardial infraction participating in the international, prospective, randomised Administration of Ticagrelor in the catheterisation Laboratory or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) trial: a prespecified analysis. BMJ Open 2017;77(9):e015241.
25. Jakobsen L, Niemann T, Thorsgaard N, et al. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention* 2012; 8(8):904-11.
26. El-Menyar A, Ahmed E, Albinali H, et al. Mortality trends in women and men presenting with acute coronary syndrome: insights from a 20-year registry. PLoS One 2013;8(7):e70066.
27. Vallianou NG, Mitesh S, Gkogkou A, et al. Chronic kidney disease and cardiovascular disease: is there any relationship? *Current Cardiology Re.* 2019;15(1):55-63.
28. Smith GL, Masoudi FA, Shlipak MG, et al. Renal impairment predicts long-term mortality risk after acute myocardial infarction. *J Am Soc Nephrol* 2008; 19(1):141-50.
29. Homorodean C, Iancu AC, Dregoesc IM, et al. Renal failure impact on the outcomes of st-segment elevation myocardial infarction patients due to a left main coronary culprit lesion treated using a primary percutaneous coronary intervention. *J Clin Med.* 2019;8(4): 565.