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Research Article

Prognostic value of renal kidney disease on the mortality of patients with acute myocardial infarction

[1]Mihai Greavu, [2]Maria Anghel, [3]Ștefan C. Vesa, [1]Mariana Rădoi

[1] Faculty of Medicine, "Transilvania" University, Brasov, Romania; [2] Emergency County Hospital, Brasov, Romania; [3] Department of Pharmacology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj Napoca, Romania.

Abstract. Background: There is a strong association between chronic kidney disease (CKD) and the risc of acute myocardial infarction (AMI). In patients with acute myocardial infarction, CKD has proven to be an important prognostic factor for a unfavorable outcome, on short, medium and long time. Aim: Evaluating the impact of chronic kidney disease, estimated trough seric levels of cystatin C, on the mortality rate at one year after acute myocardial infarction. Material and methods: This is an observational and prospective study, held between March 2013 and March 2014. The study included 127 patients diagnosed with ST elevation myocardial infarction (STEMI) and non ST elevation myocardial infarction (NSTEMI), hospitalized in the Intensive Coronary Unit of the Cardiology Department, Clinical Emergency County Hospital in Brasov. Clinical and laboratory data have been collected. The laboratory analysis included microalbuminuria, serum levels of creatinine and cystatin C as parameters of CKD. Results: We found statistically significant higher values of cystatin C (p=0,001) in the group of patients that died, compared to the patients that survived, at one year from AMI. The multivariate analysis shows cystatin C as independent predictor of mortality at one year after acute miocardial infarction (HR=2,95; p=0,04). Medium values of 24 hours microalbuminuria were higher in group 1, compared to group 2 (p<0,001). The medium value of estimated glomerular filtration rate (eGFR) was significantly smaller in group 1 compared to group 2 (p<0,001). Conclusions: High serum levels of cystain C are strong and independent predictor of one year mortality rate after acute myocardial infarction.

Key Words: serum cystatin C, acute myocardial infarction, chronic kidney disease.

Corresponding Authors: M. Greavu, e-mail: greavumihai@yahoo.com

Introduction

The correlations between chronic kidney disease (CKD) and atherosclerotic disease include both early onset and severe evolution of the atherosclerotic lessions, as well as a higher risk for acute cardiovascular events (Levey et al 1998). The high prevalence and severity of atherosclerotic lessions in patients with CKD, is explained by the often cumulative presence of hypertension, diabetes mellitus, dyslipidemia, hyperhomocysteinemia, inactive lifestyle, systemic inflammation and endothelial dysfunction (Rosengren et al 1990).

CKD is associated with high cardiovascular mortality and morbidity risk that increases in parallel with estimated glomerular filtration rate (eGRF) decreasing (Levey et al 1998).

The risk of death by myocardial infarction is higher in patients with CKD, especialy in the last stage of CKD, when acute myocardial infarction is 40% more frequent, when compared to patients with normal renal function (Levey et al 1998).

The long and medium term prognosis in patients with acute myocardial infarction, is influenced by multiple factors that include: age >75 years, previous myocardial infarction, severity of coronary lesions, pharmacologic treatment, interventional or surgical revascularisation procedures, cardiac disfunction, obesity and comorbidities (CKD, diabetes mellitus) (Smolina et al 2012).

The aim was to evaluate the impact of chronic kidney disease, estimated by seric levels of cystatin C, on one year mortality after acute myocardial infarction (AMI).

Material and methods

The study is prospective and observational and includes patients with acute myocardial infarction hospitalized in Intensive Coronary Unit of the Cardiology Department, in the Clinical Emergency County Hospital, Brasov, Romania, from March 2013 until March 2014.

The diagnosis of ST elevation myocardial infarction (STEMI) and non ST elevation myocardial infarction (NSTEMI) was established according to the recommendations of the European Society of Cardiology from universal definition of acute myocardial infarction, published in 2012 (Kristian et al 2012), the European Society of Cardiology (ESC) 2013 ESC guidelines

for the management of acute myocardial infarction in patients presenting with ST-segment elevation (Steg et al 2013) and 2012 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (Christian et al 2012).

The study protocol was aproved by the Ethics Committee of the Transilvania University from Brasov and the patients have been included only after they have signed the informed consent.

The study included 127 patients: 34 patients with STEMI (26,8%) and 93 patients with NSTEMI (73,2%). The STEMI diagnosis was established based on persistent ST-segment elevation measured at J point in two contiguous leads on the 12-lead electrocardiogram (EKG) and on the serum levels of creatine kinase (CK/CK-MB) as necrosis biomarkers. The NSTEMI diagnosis was initially sugested by the ST segment depression on the resting EKG, associated with segmental hypokinesia of the left ventricle on the two dimensional transthoracic ecocardiogram (2D-TTE) and increased serum levels of cardiac troponin T and/or CK, CK-MB.

Patients with hemodynamic instability, acute infections, unstable angina, cancer, chronic obstructive pulmonary disease stage IV Gold and hepatic cirrhosis excluded from the study.

Clinical data: age, sex, hypertension, diabetes mellitus, previous myocardial infarction, smoking, dyslipidemia, body mass index (BMI), abdominal circumference (AC) and left ventricular failure Killip class II-III were registrated at admission. (Table 1)

Left ventricular ejection fraction (LVEF) and segmental or global hypokinesia of the left ventricle were estimated on two dimensional transthoracic echocardiography (2D-TTE), using the ALOKA Prosound SSD-4000SV ecocardiograph.

Biological data included: hemoleucogram, serum levels of cistatin C, creatinine, urea, uric acid, glycemia, total cholesterol, low density lipoprotein cholesterol (LDL), high density cholesterol (HDL), triglyceride, creatin kinase (CK), CK-MB, troponin T, C reactive protein (CRP) and glycated hemoglobin (HbA1c). Troponin T was considered as necrosis biomarker from cuttof value >30 ng/ml. Serum levels of cystatin C were determined using the Tina quant test kit for Cystatin C, on the Roche/Hitachi Cobas C analyzer, with immunoturbidimetric assay. Urinary albumin was detected using the Tina quant Albumin U2 test kit, on the Roche/Hitachi Cobas C system, trough immunoturbidimetric assay.

The laboratory analysis have been performed on the Roche COBAS 6000 analyzer system in the Central Laboratory of the Clinical County Emergency Hospital in Brasov.

The chronic kidney disease was diagnosed according to the recommendations of the National Kidney Foundation at a cuttof value for eGFR of <60 ml/min/1.73 m², calculated with the Modification in Diet in Renal Disease equation (MDRD) (Levey et al 2005). The patients were followed for one year mortality rate after acute miocardial infarction. The informations were obtained by phone calls at 3, 6 and 12 months.

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS 21) software. Continuous variables are expressed as the mean standard deviation or as median values and range. The relationship between a continuous variable and a nominal variable was assessed using the T test for independent variables. The differences between the frequency of a nominal data between two groups was assessed using the chi-square test. The independent prognostic value of a variable was calculated using the Cox regression. A p value <0.05 was considered as statistically significant.

Results

At one year after acute myocardial infarction 25 patients died (19.7%) (group 1), and 102 patients survived (80.3%) (group 2). The group 1 included 18 patients with STEMI (19.4%) and 7 patients with NSTEMI (20.6%), without significant statistical differences of the mortality rate in patients with STEMI versus those with NSTEMI. The analysis of demographic data showed that the mean age of patients who died was significantly higher than the mean age of survivors (75.6±9.2 years vs. 63.1±11.1 years) (p<0.001). There were no statistically significant diferences of mortality rates between men and women with acute myocardial infarction (p=0.6) (Table 1).

The incidence of diabetes mellitus did not reach statistically significant difference in the group 1, when compared to group 2 (p=0.2). The body mass index and abdominal circumference of patients in the group 1 were significantly smaller, compared to patients in the group 2 [(26.8±5.6 versus 29.6±4.6 cm) (p=0.01)] respectively (87.7±11.5 cm versus 94±10.6 cm) (p=0.01)]. Patients with previous MI had a statistically significant higher mortality rate at one year, compared to patients without previous MI [11 (44%) versus 14 (13.7%) (p=0.002)].

The treatment in the acute phase of AMI, included double antiplatelet therapy with clopidogrel and aspirin for 91 patients (97.8%), only clopidogrel in aspirin intolerant patients for 2 patients (2.1%), high dose atorvastatin (80 mg/day) for 80 patients (89.8%), other statins in moderate dose for 9 patients (10.2%), beta blockers for 91 patients (97.8%), angiotensin converting enzyme inhibitors (ACE inhibitor) for 71 patients (76,3%) and spironolactone (25 mg/day) for 21 patients (22.6%) with sistolic disfunction of the left ventricle. Percutaneous revascularization was performed in 51 patients with STEMI (54.8%).

Treatment for NSTEMI included clexane (1mg/12hours) for 30 patients (88.2%), double antiplatelet therapy with clopidogrel and aspirin for 34 patients (100%), high dose atorvastatin (80 mg/day) for 28 patients (82.4%), other statins in moderate dose for 6 patients (17.6%), beta blockers for 34 patients (100%), angiotensin converting enzyme inhibitors (ACE inhibitor) for 29 patients (85.3%) and spironolactone (25 mg/day) for 3 patients (8.8%) from a total of 11 patients (32.1%) with sistolic disfunction of the left ventricle, defined by LVEF < 40% (Table 2).

There were no statistically significant diferences in pharmacological treatment of patients in the acute phase of STEMI and NSTEMI regarding double antiagregation, beta blockers, ACE inhibitors, spironolactone, high and medium dose statins (Table 2).

2D-TTE evaluation of the sistolic function, estimated trough LVEF%, has outlined statistically significant smaller values of LVEF in patients from group 1, compared to those from group 2 [35.2±11.1% versus 46.5±7.1%] (p<0.001). Left ventricular global hypokinesia, was significantly more frequent in group 1 compared to group 2 patients [(12 (48%) vs 13 (12.7%) (p=0.002)].

Hemoglobin levels, white blood cells, thrombocytes, fasting plasma glucose, glycated hemoglobin, total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol,uric acid and C–reactive protein showed no statistically significant differences between the two groups (Table 3).

Tabel 1. Clinical and demographic data of patients with acute myocardial infarction

Parameter	Group 1	Group 2	p value
Age	75.6±9.2	63.1±11.1	p<0.001
Diabetes mellitus	17 (23.9%)	8 (14.3%)	0.2
Previous MI	11 (44%)	14 (13.7%)	0.002
BMI	26.8±5.6	29.6±4.6 cm	0.01
AC (cm)	87.7±11.5	94±10.6	0.01
HBP	20 (20.6%)	5 (16.7%)	0.8
Smoking	12 (16.2%)	62 (83.8%)	0.3

Tabel 2. Pharmacological treatment in the acute phase of the myocardial infarction

Medication	STEMI	NSTEMI	p value
Double antiplatelet therapy	91 (97.8%)	34 (100%)	1
Beta blockers	91 (97.8%)	34 (100%)	1
ACE inhibitors	71 (76.3%)	29 (85.3%)	0.3
Spironolactone	21 (22.6%)	3 (8.8%)	0.2
High dose statins (atorvastatin 80mg/day)	80 (89.8%)	28 (82.4%)	0.5
Medium dose statins	9 (10.2%)	6 (17.6%)	0.5

Tabel 3. Laboratory parameters in patients with acute myocardial infarction

Analyzed parameter		Group 1	Group 2	p value
Hemoglobin (g/dl)		12.1±1.5	13±1.7	0.6
WBC		10000±3200	9800±3300	0.8
Thrombocytes		233000±69000	238000±73000	0.7
Fasting plasma glucose (mg/dl)		160±85.7	136±46.2	0.1
HBA1C (%)		17.2±9	7.2±2.7)	0.1
LDL-cholesterol (mg/dl)		92.6±33.4	102.9±31.2	0.1
HDL-cholesterol (mg/dl)		42.6±9.7	46.9±12.3	0.1
Triglycerides (mg/dl)		156±82	171±101	0.4
Uric acid (mg/dl)		7±2.8	6.2±2.1	0.1
CRP (mg/L)		28.7±39	22.4±31	0.4
Serum urea (mg/dl)		84.4±46.4	47.7±23.5	0.001
Urinary albumin (mg/24h)		29±18.2	8.7±11.8	<0.001
Microalbuminuria		11 (44%)	14 (13.7%)	0.002
Serum creatinine (mg/dl)		1.6±0.7	1±0.3	0.002
eGFR (ml/min/1.73m²)		47.1±20.9	72.9±22.8	<0.001
CKD stage	1	1 (4%)	25 (24.5%)	<0.001
	2	5 (20%)	45 (44.1%)	<0.001
	3	13 (52%)	29 (28.4%)	<0.001
	4	6 (24%)	2 (2%)	<0.001
	5	-	1 (1%)	<0.001
Serum Cistatina C (mg/dl)		2.6±1.4	1.2±0.6	<0.001

Table 4. Predictors of mortality at one year from the acute myocardial infarction

Variable	B	Wald	P	HR	IC 95%	
					Min	Max
Age	0.06	5.92	0.01	1.07	1.01	1.13
Previous myocardial infarction	0.36	0.53	0.4	1.44	0.54	3.83
Global hypokinesia	1.04	3.89	0.04	2.83	1	7.98
Creatinine	-0.61	1.79	0.1	0.54	0.22	1.32
Cystatin C	1.08	19.31	<0.001	2.95	1.82	4.78

Patients in group 1 versus those in group 2, have statistically significant higher values of serum creatinine (p=0.002), urea (p=0.001) and cystatin C (p=0.001). Medium values of 24 hours albuminuria were higher in patients from group 1, compared to those from group 2 [(29±18.2) versus (8.7±11.8)] (p<0.001). The incidence of microalbuminuria, defined by albuminuria of 30 to 300 mg/24 hours, was 19.6%. Microalbuminuria was found more frequent in group 1, compared to group 2 [11(44%) versus 14 (13.7%)], (p=0.002).

The medium value of eGFR was significantly smaller in patients from group 1 compared to those from group 2 [47.1±20.9 versus 72.9±22.8 (p<0.001)]. The incidence of CKD stages 2, 3 and 4 were statistically significant higher in patients from group 1, when compared to patients from group 2. (Table 3)

The multivariate analysis shows that the independent predictors of mortality one year after the acute myocardial infarction were age (>75 years) (HR 1.07; p=0.01), global hypokinesia on the 2D-TTE (HR=2.83; p=0.04) and serum cystatin C (HR=2.95; p=0.04) (Table 4). Serum level of cystatin C appear to be independent predictor of mortality (HR=2.95; p=0.04) and high values cystatin C increases the risk of mortality 2.9 times in patients with AMI.

Discussions

In our study the elderly people had an increased risk of mortality at one year after acute myocadrial infarction and age over 75 years was a strong independent predictor of mortality (HR=1.07; p=0.01). The high mortality risk of patients with acute coronary syndromes associated with old age, was already revealed in clinical studies and is used both in the GRACE (Fox et al 2006) and C-ACS (Eagle et al 2004) score to estimate the cardiovascular risc in patients with acute coronary syndromes. The literature data showed that the presence of CKD in elderly patients estimated by serum levels of cistatin C, amplifies the risk of cardiovascular death (Shlipak et al 2013). Cystatin C, a serum parameter of renal disfunction, is in elderly persons a stronger predictor of the mortality risk and cardiovascular events than is creatinine (Shlipak et al 2002).

Similarly with previous data, in our study the 1 year mortality rate after acute myocardial infarction was significantly associated with higher values of serum creatinine, serum cystatin C and albuminuria. All these parameters has been strong prognostic factors for 1 year mortality rate after acute myocardial infarction. Low eGFR (< 60 ml/min/1.73m²) was correlated with statistically significant higher risk of one year mortality after acute myocardial infarction (p< 0.001). In the multivariate analysis, only the serum levels of cystatin C were independently predictive for the mortality risk at one year after acute myocardial infarction (HR=2.95; p=0.04).

A meta-analysis on 130.099 elderly patients with acute myocadrial infarction, revealed that minor or moderate renal disfunction (eGFR 30-90 ml/min/m²), is an important and independent risk factor for mortality (Shlipak et al 2013). In this study, one year mortality was significantly higher (66%) in patients with acute myocadrial infarction and moderate CKD, compared to those without CKD (24%) (Shlipak et al 2002).

The importance of CKD in the prognois of pateints with myocardial infarction was presented in clinical studies showing on one hand that the CKD is frequently present in patients with myocardial infarction (Jassim et al 2012) and on the other hand that CKD is associated with higher mortality rates and major cardiovascular events, at one month and one year after acute myocardial infarction (Shroff & Herzog 2013).

The highest rate of death after acute myocadrial infarction, reached a peak at values of eGFR between 15 and 45 ml/min/1.73m² (Yahalom et al 2009) and these patients had a 3 to 5-fold higher risk of death, compared to patients without CKD. eGFR below 20 ml/min/1.73m² was associated with 7-fold increased risk at one year mortality after acute myocardial infarction, when compared to patients with eGRF >60 ml/min/m² (Yahalom et al 2009). Microalbuminuria was also associated with the 1 year mortailty risk after acute miocadrial infarction (Yahalom et al 2009).

Cystatin C, a protease inhibitor, sintetized in every nucleated cell, was proposed as a replacement for serum creatinine, in evaluating renal function, especially in detecting small reductions of eGFR (Nevio et al 2009).

Recent studies show cystatin C as a more sensitive marker than serum creatinine or eGFR, regarding detection of early renal dysfunction and prognosis for acute cardiovascular events (Peralta et al 2011).

In our study, serum cystatin C levels were significantly higher in group 1 compared to group 2 (p=0.001). High serum cystatin C levels associated higher mortality rates at one year after acute myocardial infarction (HR=2.95; p=0.04). Only high level cystatin C was found as independent prognostic factor of mortality, at one year from acute myocardial infarction (Zahran et al 2007). High serum cystatin C levels have been independently associated with increased risk of major cardiovascular events (Muntner et al 2002). The highest risk for major cardiovascular events was in the group of patients who had cystatin C levels >1.29 mg/L, and in these patients the risk was double (Shlipak et al 2013). Another recent study shows that cystatin C levels over the normal threshold associate a higher risk of death and reinfarction, in patients with acute myocardial infarction (Peralta et al 2011).

Conclusions

Chronic kidney disease evaluated with serum creatinine, eGFR and cystatin, is a strong prognostic factor for mortality at one year after acute myocardial infarction. Serum cystatin C levels is an independent risk factor for one year mortality after acute myocardial infarction.

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Authors

•Mihai Greavu, Faculty of Medicine, "Transilvania" University, 56 Nicolae Balcescu Street, Brasov, Romania, EU, email:greavumihai@yahoo.com

•Maria Anghel, Emergency County Hospital, 25-27 Calea Bucuresti Street, Brasov, Romania, EU

•Ştefan C. Vesa, Department of Pharmacology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 6th Pasteur Street, 400349, Cluj-Napoca, Cluj, Romania, EU, email: vdn_ro@yahoo.com

•Mariana Rădoi, Department of Cardiology, Faculty of Medicine, "Transilvania" University, 56 Nicolae Balcescu Street, Brasov, Romania, EU, email: mradoi_unitbv@yahoo.com

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