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Acute kidney injury incidence and models for mortality prediction in acute coronary syndromes

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Abstract: *Background and aim. The presence of acute kidney injury (AKI) in subjects diagnosed with acute coronary syndromes (ACS) represents a major predictor of a negative outcome.The purpose of this study is to reveal the incidence of AKI in ACS subjects and to illustrate the prognosis of these subjects, using special models for mortality prediction, based on the creatinine values and the presence of acute heart failure (AHF).*

Methods. Using multiple linear regression, several models were designed to predict the mortality including: comorbidities of the subjects, initial and highest value of the serum creatinine (sCr) during hospitalization, presence of theAHF and Killip class compared with sCr values, the last model illustrating the influence of all the previous variables.

Results. AKI had a significant incidence in the chronic kidney disease (CKD) group (53.11%). The mortality rate and the hospital readmission were higher in the CKD subjects (41.14%) versus the patients with normal kidney function (21.23%, p<0.01). The association of AKI and AHF, known as cardio-renal syndrome, was related to a negative outcome in the CKD group. The models for prediction of mortality emphasize that the age, dyslipidaemia, worst sCr, Killip class and AHF presence can be used to assess the mortality risk of patients with AKI and ACS. Previous pathological conditions such as diabetes, peripheral artery disease, coronary artery disease (CAD) and obesity, failed to achieve statistically significance for prediction of death.

Conclusions. AKI represents a serious pathological condition with a high prevalence in subjects with CKD; the association with AHF increases the risk of hospital readmission and fatal outcome.

Keywords: *acute coronary syndromes, acute kidney injury,acute heart failure, serum creatinine, predictors, mortality*

INTRODUCTION

AKI represents a pathological condition that resumes a complex interaction between various factors like subsequent renal failure, utilization of iodinated contrast substance during percutaneous coronary intervention (PCI), renal hypoperfusion caused by decreasing of the cardiac output during an ischemic event [1]. Manifestations of AKI may consist in a simple increase in sCr or severe renal failure with anuria requiring kidney replacement therapy [1]. There is a strong relationship between the renal function impairment and the CAD development, regardless the other common risk factor involvement. The prospective study realized by Jurkovitz et al. including 13,329 participants,

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without previous CAD, reflected that increased values of baseline sCr (defined as ≥1.2 mg/dL in women and ≥1.5 mg/dL in men) were associated with a high incidence of acute myocardial infarction (AMI) and death due to ischemic events, compared to normal values of the sCr [2]. The renal impairment has an important influence on the patient's outcome during cardiovascular events and a small decrease in glomerular filtration rate worsens the prognosis of these patients [3].

The complexity of the atherosclerosis process in CKD subjects is a result of the interaction between common and uncommon risk factors. Diabetes mellitus, hypertension, dyslipidaemia and smoking represent essential factors in atherosclerosis development by promoting chronic inflammation, oxidation of the low-density lipoproteins and reactive oxygen species formation [4]. Even secondary hypertension in young persons has an important role in atherosclerosis occurrence and the level of plasma renin in these subjects represents a clear indication [5, 6]. Systolic and diastolic values of the blood pressure are strongly related to alimentation in young persons and there are several actions to change the unhealthy eating habits, beginning with education regarding healthy diet from early age [7].

Various terms were attributed to AKI and that is the reason why the comparison of studies is difficult. There are more than 30 definitions of AKI and the most used are: the Risk, Injury, Failure, Loss and End-stage renal disease (RIFLE), criteria revised by the Acute Kidney Injury Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group classification.

AKI definition (according to KDIGO) expresses an increase in sCr by 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours or increase in sCr 1.5 to 1.9 times baseline value, with known or presumed abrupt onset within the prior 7 days. There are 3 stages according to the sCr values and the urine output. The first stage is consistent with sCr variations mentioned in the definition and a urine output of less than 0.5 mL/kg/h for 6-12 h, whereas the second stage involves increase in sCr 2.0 to 2.9 times baseline and a urine output of 0.5 mL/kg/h for 12 h. The last stage represents an association between increase in sCr to ≥ 4.0 mg/dL (≥ 353.6 µmol/L) or ≥ 3.0 times baseline or usage of renal replacement therapy and a urine output of less than 0.3 mL/kg/h for ≥ 24 h or anuria for ≥12 hours [8, 9, 10].

Usually, AKI remains undetected due to the fact that the onset is earlier in ACS patients and the sCr from admission represents the reference value, without actually knowing the evolution of the creatinine before hospitalization. If the sCr does not have a remarkable increase after admission, there may be an error of AKI diagnosis. New biomarkers able to early detect the AKI are required in order to initiate the preventive treatment and minimalize the renal insult [11]. The beginning of AKI is usually in the early phase of the ACS, fact that determines the late detection of this condition.

ACS represents a challenging diagnosis in CKD subjects because most of them remain asymptomatic. The explanation is suggested by the fact that uremic milieu and associated diabetic neuropathy influence the perception of pain in these patients [12, 13].Inflammation and oxidative stress represent common elements for both CKD and ACS, and the association of these diseases increases the risk to develop AKI. High levels of inflammatory markers (such as C reactive protein (CRP), fibrinogen and procalcitonin (PCT)) were found in subjects who developed AKI after PCI. Kurtul et al. revealed that PCT represents an independent factor for the development of AKI in ACS patients undergoing PCI [14]. Subjects without AKI emphasize PCT values less than 0.1 µg/L15. Gao et al. analysed 7000 PCI and illustrated that CRP levels were higher in subjects with AKI16. Gu et al. illustrated that determination of both markers, CRP and PCT, has higher predictive value in identifying subjects at high risk of AKI development. Also, the AMI is an independent risk factor involved in AKI occurrence [17].The role of antioxidants in the cardiovascular field is well known and vegetables/fruits consumption has demonstrated its effect for people at risk of cardiovascular diseases, on immunologic, clinical and antioxidant markers [18].

The main purpose of the present research is to highlight the incidence of AKI in ACS patients, and to present prediction for these patients based on particular models for mortality prognosis taking into account the presence of AHF and creatinine values.

METHOD

This study designed a retrospective single-centre analysis, which enrolled 435 patients admitted with ACS diagnosis in the Cardiology department of the Clinical Emergency County Hospital of Oradea, January 2016 - January 2018. The study lot involved 209 patients with ACS and CKD; the control lot comprised 226 patients with ACS and normal kidney function. The exclusion criteria included allergy to contrast media, exposure to the contrast media 2 days before the coronary angiography procedure, malignant conditions.The AKI patients were detected using the KDIGO classification because it contains lower values of sCr than the AKIN criteria, so the underdiagnosis of the condition was avoided.

ACS was revealed according to the Fourth Definition of the

Myocardial Infarction using the association of thoracic pain, elevated cardiac necrosis enzymes, electrocardiographic changes and imaging evidence of new regional wall motion disturbances.ST-segment elevation myocardial infarction (STEMI) was defined due to the presence of persistent ST-segment elevation more than 1 mm in two contiguous leads with the exception of precordial leads that require an elevation of 1.5 mm in women, more than 2.5 mm in men under 40 years-old and less than 2 mm in men older than 40 years. Myocardial infarction in subjects with previous left bundle branch was revealed due to Sgarbossa's criteria. Non-ST-segment elevation myocardial infarction (N-STEMI) illustrates either a ST-segment depression ≥0.5 mm in two contiguous leads or deep inverted T wave more than 1 mm, along with elevated myocardial necrosis enzymes. Unstable angina (UA) expresses cardiac necrosis enzymes in normal limits associated with T negative wave, ST-segment depression or transitory ST-segment elevation [19]. Left ventricle ejection fraction (LVEF) was assessed using the Simpson's method. The normal value was considered between 50-72% in men and 52-74% in women [20].

Cardiac necrosis enzymes, cTnI (cardiac troponin I) and hscTnI (high-sensitive cardiac troponin I), were tested and abnormal values were defined as elevated when the result showed at least one value above the upper limit of the 99th percentile. Normal ranges were considered whenthe values were lower than 0.04 ng/mL for cTnI and 29 ng/L for hscTnI. Serial measurements were required to exclude thediagnosis of myocardial injury [21].

Killip Kimball classification was assessed in each patient with STEMI and the four classes. The first class illustrated subjects without signs of cardiac decompensation, the second class included patients with rales, third heart sound and increased jugular venous pressure. The third class was consistent with acute pulmonary oedema and the last stage revealed subjects with cardiogenic shock [22].

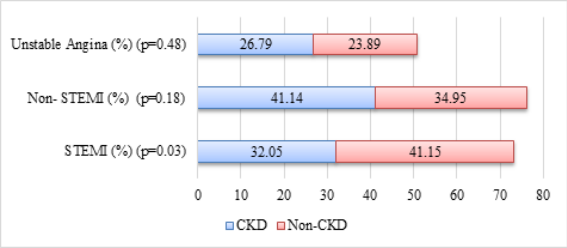
The statistical analysis was performed using Biostat software. Chi-square test was used when comparing prevalence in the two-groups, while Anova test was used to compare the mean values of certain parameters in the two groups. Univariate and multivariate regressions were done to assess the factors that correlate with the risk of death. A value of p<0.0 was considered statistically significant.

This research was performed respecting the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and it was approved by the Ethics Committee of the Clinical County Emergency Hospital of Oradea, Bihor County, Romania (decision no. 30088/December 10th, 2019); each patient included in the study signed the informed consent form.

RESULTS

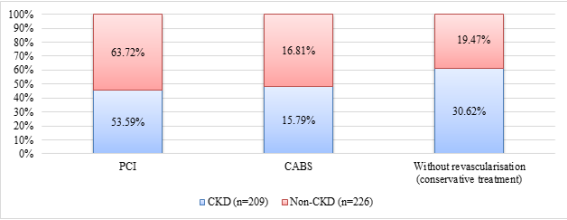
The prevalence of the common risk factors and associated comorbidities was higher in the CKD lot. Conditions like hypertension, diabetes mellitus, dyslipidaemia and peripheral artery disease were present in an increased proportion in CKD subjects in comparison with patients without CKD (84.21% vs 63.27%, p<0.01; 58.85% vs 33.62%,p<0.01; 60.09% vs 49.95%, p=0.02; 20% vs 4.9%, p<0.01).The distribution of the ACS types was different between the two lots. STEMI was characteristic in subjects without CKD whereas the CKD lot revealed mostly N-STEMI cases, UA had a similar incidence in both CKD and non-CKD lots (Figure 1).

Figure 1: Categories of coronary syndrome according to the presence/absence of CKD



Myocardial interventional revascularization through PCI and stent implantation represented the therapeutic option for 53.59% of CKD subjects and 63.72% non-CKD patients (p=0.03). Coronary artery bypass surgery (CABS) was performed in 15.79% of CKD subjects, whereas the non-CKD lot had a proportion of surgical myocardial revascu1arization of 16.81% (p=0.77). The use of conservative treatment instead of PCI, known as renal nihilism, was objectified mostly in the CKD lot (p<0.01) (Figure 2).

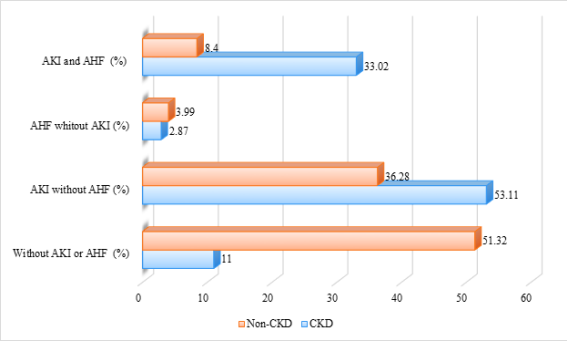
Figure 2: Treatment of ACS according to the presence/absence of CKD



AKI has occurred in the CKD lot, revealing statistically significance (p<0.01). The association of two pathological conditions, such as AKI and AHF, had a major impact in subjects' outcome and was revealed in the CKD group (p<0.01). The uncomplicated evolution of the ACS cases was

noticed in patients with normal kidney function (p<0.01) (Figure 3).

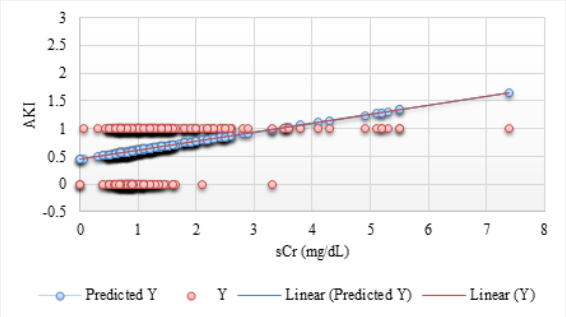
Figure 3: Presence of AKI or AHF according to the presence/ absence of CKD



Deteriorated LVEF was noticed in a higher proportion in CKD lot, compared to patients without CKD (23.5% vs 20.17%, p=0.4). The average value of sCr was higher in the CKD lot (1.66 mg/dL vs 0.8, p<0.01), the standard deviation (Q1=1.01, Q2=0.20). Another important parameter was the worst value of the sCr which revealed a high level in the CKD lot with statistical significance (2.71 mg/dL vs 1.1 mg/dL, p<0.01), standard deviation (Q1=2.11, Q2=0.36).The analysis of the average sCr variation illustrated an increased value in the CKD group (1.03 mg/dL vs 0.3 mg/dL, p<0.01).The mortality rate was statistically significant in CKD subjects compared to patients with normal kidney function (13.39% vs 6.1%, p<0.05, SD CKD 8.39-17.61, SD non-CKD 4.39-7.69). Killip class assessment revealed that most of the subjects without CKD had first Killip class at admission (p<0.01), whereas the CKD patients were included in the third and fourth Killip classes (p<0.01).

The initial value of sCr illustrated importance in univariate analysis and predicted the development of AHF and AKI (p<0.01) (Figure 4, Figure 5, Table 1).

Figure 4: Correlation between worst value of sCr (mg/dL) and AKI development



Models for mortality prediction were designed using multivariate analysis and including different factors to demonstrate the impact of AKI and other comorbidities or biomarkers regarding the outcome of patients with ACS (Table 2). The first model, based on the medical history and the associated cardiovascular risk factors of the subjects, illustrated that only the age and dyslipidaemia reached statistical importance to predict the mortality risk in ACS subjects with and without CKD (p=0.0404, p=0.0332).

Figure 5: Correlation between worst value of sCr (mg/dL) levels and AHF development

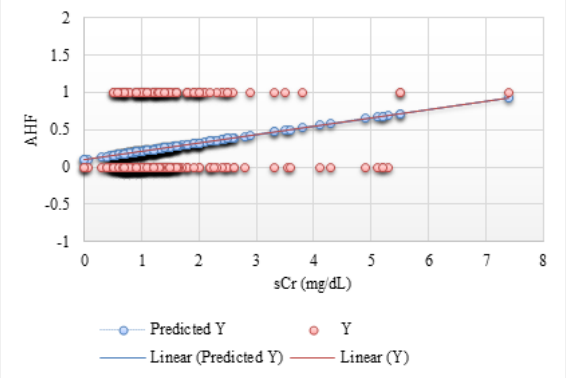


Table 1: Parameters of linear regression

	Coefficient	Standard error	LCL	UCL	t Stat	p value
Between worst value of sCr (mg/dL) and AKI						
Intercept	0.4489	0.0389	0.3724	0.5253	11.5427	*0.0000
Worst value of sCr (mg/dL)	0.1619	0.0263	0.1102	0.2136	6.1518	1.7451E-9
Between sCr (mg/dL) and AHF						
Intercept	0.1005	0.0352	0.0314	0.1696	2.8576	*0.0045
Worst value of sCr (mg/dL)	0.1120	0.0238	0.0652	0.1587	4.7053	3.4162E-6

**p<0.05, respectively p<0.001; LCL –low confidence limit; UCL–upper confidence limit; sCr – serum creatinine*

Diabetes, hypertension, smoking condition, history of peripheral artery disease, stroke did not predict the risk of death in the presented model. The second model included an analysis regarding the mortality risk of the study groups based on the presence of complications and biomarkers values. The presence of AHF and Killip class were statistically significant in anticipating the fatal outcome (p=0.0002, p<0.01). Other parameters like sCr value, age, troponin, LVEF

failed to demonstrate their role in predicting the mortality. The third model evaluated the difference between baseline sCr and the worst value of sCr in identifying the patient's outcome. The worst value of sCr was the most important factor in mortality prediction in this model (p=0.0117). The fourth model represented an evaluation of all the variables in detecting the mortality risk. The Killip class and the AHF demonstrated statistical importance (p=0.0132, p= 0.0000).

Table 2: Prediction of mortality risk using multivariate analysis, based on 3 models

Parameter	Coefficient	Standard error	p value
Model 1. Associated cardiovascular risk factors and comorbidities			
Intercept	-0.0037	0.1521	0.9805
Age	0.0027	0.0013	*0.0404
Gender	-0.0004	0.0342	0.9918
BMI (kg/m^2)	-0.0030	0.0034	0.3700
Smoking	0.0137	0.0187	0.4656
Hypertension	-0.0342	0.0348	0.3270
Diabetes mellitus	-0.0111	0.0162	0.4945
CKD	0.0498	0.0327	0.1288
Anaemia	0.0496	0.0328	0.1318
Peripheral artery disease	0.0866	0.0469	0.0661
Chronic obstructive pulmonary disease	0.0131	0.0583	0.8229
Stroke	-0.0728	0.0491	0.1389
CAD	0.0020	0.0117	0.8651
Model 2. Complications and paraclinical results			
Intercept	-0.2572	0.0972	*0.0085
Age	0.0009	0.0010	0.3625
Initial value of sCr (mg/dL)	-0.0066	0.0328	0.8410
Worst value of sCr (mg/dL)	0.0144	0.0176	0.4138
AKI	-0.0175	0.0271	0.5200
AHF	-0.2284	0.0598	*0.0002
cTnI (ng/mL)	0.0057	0.0286	0.8426
Killip class	0.2300	0.0303	*<0.001
Decreased LVEF	0.0431	0.0322	0.1818
Model 3. Initial sCr and worst value of sCr			
Intercept	0.0176	0.0249	0.4791
Initial sCr (mg/dL)	-0.0027	0.0350	0.9375
Worst value of sCr (mg/dL)	0.0439	0.0173	*0.0117

**p<0.05, respectively p<0.001; BMI – body mass index; CKD – chronic kidney disease; CAD – coronary artery disease; AKI – acute kidney injury; AHF – acute heart failure; ctnI –cardiac troponin I; LVEF – left ventricular ejection fraction; sCr – serum creatinine.*

DISCUSSIONS

The present study outlines two significant ideas: (1) The serial determination of sCr is essential in identifying subjects with AKI and special attention should be paid to subjects with CKD undergoing the coronary procedure; (2) The presence of AKI in patients with ACS and CKD can be a fatal prognosis, especially when associated with AHF. Despite following accurate indications regarding coronary imaging, like the use of a low-osmolarity contrast agent (600-800 mOsm/kg) and the corresponding post-procedural hydration associated with diuresis stimulation, the incidence of AKI varies from 5% to 55% [1, 23, 24]. The variable incidence resides in variations of the nomenclature of this term [25].

As there is no safe and highly efficient prevention method for AKI, it is considered necessary to develop prediction scores to identify high-risk patients [26]. A first element that should be included is the Killip class, evaluated upon admission to the hospital, along with the presence of AHF. These elements should be identified particularly for CKD subjects, as multivariate analysis demonstrates the role of independent risk factors for the risk of death in these patients. The reduction of the number of functional nephrons, evidenced by the initial sCr analysis and the worst value of the sCr, together with an increased rate of reduced

LVEF are major predictors of AKI and AHF occurrence, an association known as cardio-renal syndrome [27].

Common cardiovascular risk factors have failed to outline the risk of mortality in multivariate analysis, except for dyslipidaemia, since in the case of CKD there are also factors specific to the uremic environment that significantly influence the prognosis of these patients. Early myocardial revascularization reduces the risk of AHF. A recent study confirms the importance of this therapeutic method, especially in subjects with N-STEMI and CKD, that associate increased values of cardiac biomarkers, such as the N-terminal fragment of the brain natriuretic peptide (N-terminal pro b-type natriuretic peptide, NT-proBNP, BNPT) or hscTnI, or a Killip class three or four [28]. For patients with ACS undergoing PCI, an independent predictor of developing AKI is the level of NT-proBNP at admission, being connected with high costs, extended hospitalization, high rates of terminal-stage renal failure, repeat revascularization, myocardial infarction and early and late mortality [29]. LVEF shows low values in subjects with ACS and CKD due to the increased incidence of multivariate CAD and especially to the impairment of left coronary artery trunk. Choosing the method of myocardial, interventional or surgical revascularization should consider the possibility of resolving all significant coronary lesions, the complexity of CAD and the surgical risk for the subjects [30].

The increased mortality evidenced in the group of subjects with CKD is explained by the increased incidence of AKI in these subjects. The mean hospitalization period was longer for patients with ACS and CKD who developed AKI, highlighting the severity of this complication (15.71 days vs. 13.15 days, $p < 0.01$). For patients with STEMI, accentuated oxidative stress, sympathetic activation and pronounced inflammatory response were found to synergistically accelerate AKI [31]. The most powerful independent predictor of mortality within hospital in case of dangerous settings like for STEMI associated with cardiogenic shock was identified to be AKI [32].

A recent and further argument of the way AKI influences the long-term effect for patients suffering from STEMI subjected to primary PCI is presented by Narula et al. The 3-year follow-up revealed that the mortality rate for patients suffering from AKI was 16%, while for those without AKI it was 4%. As for the association of severe ischemic cardiac side effects and serious bleeding, the intensification of the side effects was more accentuated after three years, being of 40% for subjects with AKI and about 25% for patients without AKI. Corroborated, these data show that AKI evolution influences the complete prognosis of ACS patients [33]. Throughout primary PCI for STEMI, increased contrast volume is connected with increased levels of AKI and mortality, the contrast ratio and contrast volume determining AKI evolution [34]. A general complication in the case of patients suffering from shock and myocardial infarction is nephropathy, as recently revealed by a CULPRIT-SHOCK study that showed a high percentage of subjects (11.6-16.4%) who needed renal replacement therapy [35].

The decrease of renal mass is thought to be the main pathophysiology that is associated with CKD, AKI and the end stage renal disease. Considering these interesting findings and the fact that the common therapies do not influence the short-term prediction in AKI, supplementary preventive actions meant to ameliorate the health status for AKI survivors are extremely important. There is general evidence that most of the patients suffering from AKI are not regularly surveyed by nephrologists and the current clinical practice does rarely include follow up evaluation for AKI, dealing with this issue representing a considerable option for important change and better caring for this category of population [36]. Even patients with mild and moderate AKI, which in most cases is short lived and clinically reversible renal failure, had an elevated risk of death after hospitalization that did not dissipate over time. These conclusions arenovel and do not support the conventional teaching that AKI in its mild-form is inconsequential [37].

CONCLUSIONS

AKI negatively influences the short- and long-term prognosis of subjects diagnosed with ACS. CKD and AHF are other negative predictors of ACS evolution and their association with AKI has shown the highest mortality rate. Although it is not an accurate marker, the initial sCr and the worst value of sCr can be used in AKI detection to establish appropriate therapeutic measures. New predictive scores able to identify AKI in a timely manner are necessary, considering the fatal prognosis for patients with ACS and CKD.Early and complete myocardial revascularization in ACS is an optimal method, which decreases the risk of developing AHF and AKI, known as cardio-renal syndrome.

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