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Inflammatory Cytokines as Risk Factors for Mortality After Acute Cardiac Events

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ABSTRACT

Introduction: Inflammatory markers have been identified as potential indicators of future adverse outcome after acute cardiac events. **Aim:** This study aimed to analyze baseline inflammatory cytokines levels in patients with acute heart failure (AHF) and/or acute coronary syndrome (ACS) according to survival. The main objective was to identify risk factors for mortality after an episode of AHF and/or ACS. **Methods:** In this prospective longitudinal study 75 patients with the diagnosis of AHF and/or ACS were enrolled. Baseline laboratory and clinical data were retrieved. Serum and urine interleukin-6 (IL-6) and interleukin-18 (IL-18) levels, plasma B-type natriuretic peptide (BNP) and serum cystatin C values were determined. The primary outcome was in-hospital mortality while secondary outcome was six-month mortality. **Results:** Median serum and urine IL-6 levels, serum and urine IL-18 levels, as well as median concentrations of plasma BNP and serum cystatin C, were significantly increased in deceased in comparison to surviving AHF and/or ACS patients. Univariate Cox regression analysis identified serum IL-6, serum IL-18, urine IL-6, urine IL-18 as well as serum cystatin C and Acute Physiology and Chronic Health Evaluation (APACHE) II score as risk factors for mortality after an episode of AHF and/or ACS. Multivariate Cox regression analysis revealed that only serum IL-6 is the independent risk factor for mortality after acute cardiac events (HR 61.7, 95% CI 2.1-1851.0; p=0.018). **Conclusion:** Present study demonstrated the strong prognostic value of serum IL-6 in predicting mortality of patients with AHF and/or ACS.

Key words: acute heart failure; acute coronary syndrome; inflammatory cytokines; interleukin-6; mortality.

1. INTRODUCTION

Risk stratification of mortality following acute heart failure (AHF) and/or acute coronary syndrome (ACS) is a very important issue. Heart failure remains the leading cause of death world-wide causing a significant burden on health care systems across the globe. Acute coronary syndrome is a spectrum of diseases comprising unstable angina (UA), ST segment elevation myocardial infarction (STEMI) and non ST segment elevation myocardial (NSTEMI). These life-threatening disorders remain a source of high morbidity and mortality despite advances in treatment (1, 2).

For patients experiencing acute cardiac events, the best time to predict their prognosis is during hospitalization. Previous studies have identified individual risk factors associated with poor outcomes. Standard risk markers were male gender, older age, comorbidities such as diabetes mellitus, vascular disease and chronic kidney disease (CKD) as well as low sodium and albumin levels (3). Recently, inflammatory markers have been identified as potential indicators of future adverse events following AHF (1). Interleukin-6 (IL-6) is one of the inflammatory markers of local coronary plaque and the peripheral blood cycle, promoting the occurrence of atherosclerosis development and plaque rupture and is known to be elevated in patients with coronary artery disease (CAD) (4). Despite his potential role in the occurrence and development of

ACS, the prognostic value of IL-16 in patients with ACS has been rarely investigated (5). An increase of another inflammatory cytokines, interleukin-18 (IL-18) activity, has been correlated with a number of human pathologies including acute myocardial infarction, heart failure, and pressure-overload (6). The IL-18 is of particular interest as a predictor of adverse events after acute cardiac events, because both clinical and experimental studies have supported its role in atherosclerotic plaque progression and destabilization (7).

There is a need for reliable prediction tool for identification of patients with high mortality risk after an episode of an acute cardiac event.

2. AIM

The present study aimed to analyze baseline inflammatory cytokines levels in patients with AHF and/or ACS according to survival status. The main objective was to identify risk factors for mortality after an episode of AHF and/or ACS.

3. MATERIALS AND METHODS

This prospective longitudinal study was performed in the Clinical Center University of Sarajevo (CCUS) at Clinic for Heart Disease and Rheumatism and Clinic for Nephrology. The study protocol was approved by Human Research Ethics Committee of the CCUS. All patients gave informed and written consent to participate in the study. In total, 75 patients with AHF and/or ACS were enrolled consecutively. Patients were followed up for six months starting from the first day of hospital admission by the visit every two months or telephone calls. The inclusion criteria were adult patients with the diagnosis of AHF and/or ACS. Exclusion criteria were as follows: unable to give written informed consent, duration of hospital stay ≤24 hours, pediatric patients (age ≤18 years), history of the end-stage renal disease (ESRD) or prior kidney transplantation and presence of active infections.

Acute coronary syndromes included the diagnosis of UA, NSTEMI, and STEMI. Acute myocardial infarction was defined according to the third universal definition of myocardial infarction (8). Diagnosis of AHF was based on European Society of Cardiology (ESC) guidelines (9). Clinical assessment of severity of illness was evaluated using Acute Physiology and Chronic Health Evaluation (APACHE) II score (10). Estimated glomerular filtration rate (eGFR) was calculated using Modification of the Diet in Renal Disease (MDRD) equation (11). Demographic information included age, sex, body mass index (BMI) and length of hospital stay. Clinical data included primary diagnosis, comorbidities (diabetes mellitus, hypertension, CKD, history of cerebrovascular accidents, previous heart failure). The following laboratory values were obtained at admission: blood urea nitrogen (BUN), serum creatinine, and hemoglobin. The primary outcome was in-hospital mortality, while secondary outcome was six-month mortality. Telephone follow-up was used to assess six-month mortality. Quantitative determinations of IL-6 and IL-18 in serum and urine of the patients were performed by Human Instant Elisa Kit (eBioscience). The microparticle immunoassay method was used for determination of plasma B-type natriuretic peptide (BNP) levels (Abbott Laboratories) and Human Cystatin C Elisa Kit for the measurement of the concentration of cystatin C in serum.

The statistical analysis was performed using SPSS for windows version 16.0. Categorical variables were expressed as counts and percentage. Continuous variables were expressed as means ± standard deviation or medians (with 25th and 75th percentiles) values. Mann-Whitney U test used to compare variables with non-normal distribution. Univariate and multivariate Cox proportional regression analyses were performed to assess the relationship between variables and overall mortality. A p value of <0.05 was considered statistically significant.

4. RESULTS

In total, 75 patients with acute cardiac events were enrolled and followed-up for six months. Patients characteristics are listed in Table 1. The mean age was 65.5±11.6 years and 60.5% were men. The median duration of hospitalization was 12.0 (10.0-15.0) days. The most common cause of hospital admission was AHF which was present

Age, years	65.5±11.6
Male, n (%)	52 (60.5)
Current smokers, n (%)	33 (56.9)
Length of hospital stay, days	12.0 (10.0-15.0)
BMI (kg/m^2)	28.4±1.9
APACHE II score	9.0±3.5
AHF, n (%)	37 (49.3)
ACS, n (%)	24 (32.0)
AHF and ACS, n (%)	14 (18.7)
Pre-existing CKD, n (%)	20 (26.7)
Diabetes mellitus, n (%)	23 (30.7)
Hypertension, n (%)	48 (64.0)
Stroke, n (%)	10 (13.3)
Previous heart failure, n (%)	12 (16.0%)
Previous myocardial infarction, n (%)	22 (29.3%)
Anaemia, n (%)	13 (17.3)
BUN at admission, mmol/L	6.95 (5.5-8.9)
BUN at discharge, mmol/L	7.1 (5.8-9.6)
Serum creatinine at admission, µmol/L	81.5 (69.3-96.8)
Serum creatinine at discharge, µmol/L	80.0 (71,0-98.8)
Baseline eGFR, mL/min/1,73 m^2	86.2±23.3
eGFR at discharge, mL/min/1,73 m^2	80.5±24.6
MAP, mm Hg	102±20
Heart rate, bpm	98±30
Atrial fibrilation, n (%)	28 (37.3)
Left ventricular hypertrophy, n (%)	52 (69.3)
Left ventricular EF, %	41.5±10.2
Left ventricular EF <50%, n (%)	45 (60)
In-hospital mortality, n (%)	4 (5.3)
Six-month mortality, n (%)	7 (9.9)

Table 1. Characteristics of patients with acute heart failure and/or acute coronary syndrome. Data are presented as numbers and proportions, means and standard deviation or median and interquartile range. BMI – body mass index; APACHE–Acute Physiology and Chronic Health Evaluation; AHF – acute heart failure; ACS – acute coronary syndrome; CKD – chronic kidney disease; BUN–blood urea nitrogen; eGFR–estimated glomerular filtration rate; MAP–mean arterial pressure; bpm – beats per minute; EF – ejection fraction.

	Total (n=75)	Survivors (n=64)	Non-survivors (n=11)	p-value
Plasma BNP, pg/mL	358.5 (162.3-878.6)	288.1 (138.2-797.6)	989.6 (380.9-1037.6)	0.008
Serum cystatin C, mg/L	1.08 (0.87-1.28)	1.02 (0.85-1.22)	1.48 (1.1-1.75)	0.004
Serum IL-18, pg/mL	46.7 (12.27-154.2)	37.1 (0.0-89.5)	256.1 (162.4-301.5)	<0.001
Urine IL-18, pg/mL	0.00 (0.0-55.7)	0.0 (0.0-28.7)	202.1 (0.0-226.8)	0.001
Serum IL-6, pg/mL	2.16 (0.69-6.23)	1.52 (0.55-5.3)	10.3 (2.3-19.4)	0.007
Urine IL-6, pg/mL	1.46 (0.4-3.74)	1.06 (0.37-3.21)	15.0 (2.8-17.5)	<0.001

Table 2. Baseline serum and urine biomarker levels in patients with acute heart failure and/or acute coronary syndrome by survival. BNP–B-type natriuretic peptide; IL-18 – interleukin-18; IL-6 – interleukin-6.

in 49.3% of patients. Acute coronary syndrome and ACS associated with AHF were present in 32.0% and 18.7% of cases, respectively. A relatively high percentage of comorbidities were present, including 64% of patients with hypertension, 30.7% with diabetes and 26.7% with preexisting CKD. The admission mean arterial pressure (MAP) was 102±20 mm Hg and heart rate 98±30 beats per minute (bpm). Left ventricular ejection fraction (EF) was 41.5±10.2, with 45 patients (60%) having a left ventricular EF <50% and 52 patients (69.3%) having left ventricular hypertrophy. Overall mortality was 15.2%.

Table 2 shows biomarkers concentrations measured at admission and grouped by survival. Median plasma BNP levels were significantly increased in deceased in comparison to surviving patients with AHF and/or ACS (989.6 (380.9-1037.6) vs. 288.1 (138.2-797.6) pg/mL; p=0.008). Serum cystatin C concentration was significantly higher in acute cardiac patients who died in comparison to those who survived (1.48 (1.1-1.75) vs. 1.02 (0.85-1.22) mg/L; p=0.004). Median serum IL-18 (256.1 (162.4-301.5) vs. 37.1 (0.0-89.5) pg/mL; p<0.001) and urine IL-18 levels (202.1 (0.0-226.8) vs. 0.0 (0.0-28.7) pg/mL; p=0.001) were significantly higher in non-survivors in comparison to survivors. Median serum IL-6 values were significantly increased in deceased (10.3 (2.3-19.4) pg/mL) in comparison to surviving patients (1.52 (0.55-5.3) pg/mL) (p=0.007). Finally, median levels of urine IL-6 were higher in acute cardiac patients who died (15.0 (2.8-17.5) pg/mL) in comparison to those who survived (1.06 (0.37-3.21) pg/mL) (p<0.001).

Univariate analysis identified six variables as mortality prediction valuable (Table 3). Risk factors for overall (in-hospital and six-month) mortality in patients with AHF and/or ACS were serum IL-6 (HR 12.9, 95% CI 2.2-77.0; p=0.005) and serum IL-18 (HR 72.7, 95% CI 1.27-3.9; p=0.004), urine IL-6 (HR 13.2, 95% CI 2.1-82.7; p=0.006) and urine IL-18 (HR 413.7, 95% CI 1.1-158433.8; p=0.048) as well as serum cystatin C (HR 202.1, 95% CI 1.24-3284.3; p=0.041) and APACHE II score (HR 1.5, 95% CI 1.13-1.96; p=0.004). Multivariate Cox regression analysis revealed that only serum IL-6 is the independent predictor of overall mortality in patients with acute cardiac events (HR 61.7, 95% CI 2.1-1851.0; p=0.018).

Univariate Cox regression analysis for overall mortality in patients with acute heart failure and/or acute coronary syndrome			
Variables	HR	95% CI for HR	p-value
Serum IL-18	72.7	1.27-3.9	0.004
Urine IL-18	413.7	1.1-158433.8	0.048
Serum IL-6	12.9	2.2-77.0	0.005
Urine IL-6	13.2	2.1-82.7	0.006
Plasma BNP	3.7	0.8-17.4	0.1
Serum cystatin C	202.1	1.24-3284.3	0.041
APACHE II score	1.5	1.13-1.96	0.004
Age	1.01	0.95-1.1	0.76
Multivariate Cox regression analysis for overall mortality in patients with acute heart failure and/or acute coronary syndrome			
Serum IL-6	61.7	2.1-1851.0	0.018

Table 3. Cox regression analysis for overall mortality in patients with acute heart failure and/or acute coronary syndrome. HR – hazard ratio; CI – confidence interval; IL-18 – interleukin-18; IL-6 – interleukin-6, BNP–B-type natriuretic peptide; APACHE–Acute Physiology and Chronic Health Evaluation.

5. DISCUSSION

This study confirmed that inflammatory cytokines IL-6 and IL-18 in serum and urine, as well as serum cystatin C and plasma BNP, are associated with increased risk for mortality after acute cardiac events. In multivariate regression analysis, only serum IL-6 proved to be the independent predictor of mortality after AHF and/or ACS.

The study cohort consisted of 75 patients with the diagnosis of AHF and/or ACS. The patients characteristics tended to be similar to those treated in other coronary tertiary care centers. Patients were old and less likely to be women. However, they had higher left ventricular EF and less prevalence of previous heart failure than reported (12). Analysis of values of inflammatory cytokines, serum cystatin C and plasma BNP by survival showed significantly elevated biomarkers levels in deceased patients in our study group. Interleukin-6 is a pleiotropic cytokines with a broad range of humoral and cellular immune effects and it is produced not only by immune cells but also by cardiovascular components, such as endothelial cells, vascular smooth-muscle cells, and ischaemic myocytes. Elevated levels of IL-6 have been found in patients suffering from acute and chronic heart failure (1). Prognostic role of IL-16 was confirmed in patients with AHF (13). The serum level of IL-6 was also associated with unfavorable clinical outcomes in patients hospitalized for UA and STEMI (14). In accordance with these findings, the present study demonstrated significantly elevated levels of serum IL-6 in deceased AHF and/or ACS patients. Furthermore, serum IL-6 was strong independently associated with mortality after acute cardiac events. Filtration of circulating serum cytokines by the glomerulus is expected since most cytokines are between 10 to 30 kD. Cytokines, like other proteins, are filtered at the glomerulus and then endocytosed and metabolized by the proximal tubule. Increased urine IL-6 can diagnose acute kidney injury (AKI) post-cardiopulmonary bypass probably due to the impaired proximal tubule

metabolism (15). However, to our best knowledge, prognostic role of urine IL-6 for predicting mortality in acute cardiac patients was not yet investigated. Our results showed significantly elevated levels of urine IL-6 in acute cardiac patients who died in comparison to survivors implying the possible prognostic value of urine IL-6 for mortality after an acute cardiac event. Nevertheless, the larger multicentric investigation is needed to evaluate the predictive value of urine IL-6 in patients with AHF and/or ACS. Although serum and urine IL-18 levels were independently predictive of poor clinical outcome in Intensive Care Unit (ICU) population (16, 17), investigations regarding prognostic role of IL-18 in patients with heart diseases are scarce. Recently, there is growing evidence for a role of IL-18 in myocardial infarction and heart failure. In animal models of acute myocardial infarction, IL-18 regulates cardiomyocyte hypertrophy and induces cardiac contractile dysfunction and extracellular matrix remodeling. In patients, high IL-18 levels correlate with increased risk of developing cardiovascular disease (CVD) and with a worse prognosis in patients with established CVD. Increased IL-18 correlate with HF severity and predict adverse prognosis (6). Present study also confirmed the association of baseline serum and urine IL-18 with adverse outcome after acute cardiac events. The negative prognostic role of serum IL-18 can be related with possible plaque destabilization due to increased expression of IL-18 in human atherosclerotic plaques. In patients with previous myocardial infarction, the risk of restenosis was increased in patients with elevated IL-18 levels after percutaneous coronary intervention for acute myocardial infarction (7). Cystatin C is an endogenous cysteine proteinase inhibitor produced by nucleated cells. Because of its low molecular weight it is freely filtrated by glomerulus and reabsorbed by renal tubules and it has been proposed as an early and sensible marker of glomerular function. No active tubular secretion or significant extrarenal elimination of cystatin C occurs. In the setting of AHF, cystatin C independently predicts death or heart failure rehospitalization with greater accuracy than creatinine and eGFR (3). Cystatin C is also an important prognostic factor of poor outcome in patients with ACS (18). In accordance with previous reports, our results identified serum cystatin C as the risk factor for mortality after AHF and/or ACS by univariate regression analysis. However, multivariate analysis has not confirmed this finding, probably due to the relatively small proportion of adverse events in our cohort of acute cardiac patients. Furthermore, although our study confirmed the association between increased plasma BNP levels and mortality after acute cardiac events which is in line with negative prognosis associated with BNP among patients with AHF that has been demonstrated earlier (19), we failed to show prognostic value of BNP in regression analysis.

6. CONCLUSION

The present study demonstrated the strong prognostic value of serum IL-6 for predicting mortality in patients with AHF and/or ACS. It also revealed a significant association of high levels of serum IL-18, urine IL-6, urine IL-18, plasma BNP and serum cystatin C with mortality after acute cardiac events. Combining measurements of inflammatory cytokines, serum cystatin C, and plasma BNP seem a promising tool in the prognostic assessment of these patients.

• Conflict of interest: none declared.

REFERENCES

1. Iqbal N, Wentworth B, Choudhary R, De La Parra Landa A, Kipper B, Fard A, et al. Cardiac biomarkers: New tools for heart failure management. Cardiovasc Diagn Ther. 2012; 2(2): 147-64.
2. Masic I, Dilic M, Raljevic E, Vulic D, Mott D. Trends in cardiovascular diseases in Bosnia and Herzegovina and perspectives with HeartScore Programme. Med Arh. 2010; 64(5): 260-3.
3. Pascual-Figal DA, Caballero L, Sanchez-Mas J, Lax A. Prognostic markers for acute heart failure. Expert Opin Med Diagn. 2013; 7(4): 379-92.
4. Su D, Li Z, Li X, Chen Y, Zhang Y, Ding D, Deng X, Xia M, Qiu J, Ling W. Association between serum interleukin-6 concentration and mortality in patients with coronary artery disease. Mediators Inflamm. 2013; 2013: 726178.
5. Wang XH, Liu SQ, Wang YL, Jin Y. Correlation of serum high-sensitivity C-reactive protein and interleukin-6 in patients with acute coronary syndrome. Genet Mol Res. 2014; 13(2): 4260-6.
6. O'Brien LC, Mezzaroma E, Van Tassell BW, Marchetti C, Carbone S, Abbate A, et al. Interleukin-18 as a therapeutic target in acute myocardial infarction and heart failure. Mol Med. 2014; 20: 221-9.
7. Hartford M, Wiklund O, Hultén LM, Persson A, Karlsson T, Herlitz J, et al. Interleukin-18 as a predictor of future events in patients with acute coronary syndromes. Arterioscler Thromb Vasc Biol. 2010; 30(10): 2039-46.
8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD on behalf of the Joint European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Health Federation (ESC/ACCF/AHA/WHF) Task Force for the Redefinition of Myocardial Infarction. Third universal definition of myocardial infarction. Eur Heart J. 2012; 28: 2525-38.
9. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33: 1787-847.
10. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985; 13(10): 818-29.
11. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of the Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007; 53(4): 766-72.
12. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, et al. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail. 2008; 10(2): 188-95.
13. Pudil R, Tichý M, Andrýs C, Rehácek V, Bláha V, Vojácek J, et al. Plasma interleukin-6 level is associated with NT-proBNP level and predicts short- and long-term mortality in patients with acute heart failure. Acta Medica (Hradec Kralove). 2010; 53(4): 225-8.
14. Fan ZX, Hua Q, Tan J, Gao J, Liu RK, Yang Z. Interleukin-6 but not soluble adhesion molecules has short-term prognostic value on mortality in patients with acute ST-segment elevation myocardial infarction. African Journal of Biotechnology. 2011; 10(8): 1454-9.
15. Dennen P, Altmann C, Kaufman J, Klein CL, Andres-Hernando A, Ahuja NH, et al. Urine interleukin-6 is an early biomarker of acute kidney injury in children undergoing cardiac surgery. Crit Care. 2010; 14(5): R181.
16. Lin CY, Chang CH, Fan PC, Tian YC, Chang MY, Jenq CC, et al. Serum interleukin-18 at commencement of renal replacement therapy predicts short-term prognosis in critically ill patients with acute kidney injury. PLoS One. 2013; 8(5): e66028.
17. Siew ED, Ikizler TA, Gebretsadik T, Shintani A, Wickersham N, Bossert F, et al. Elevated urinary IL-18 levels at the time of ICU admission predict adverse clinical outcomes. Clin J Am Soc Nephrol. 2010; 5(8): 1497-505.
18. Taglieri N, Fernandez-Berges DJ, Koenig W, Consuegra-Sanchez L, Fernandez JM, Robles NR, et al; SIESTA Investigators. Plasma cystatin C for prediction of 1-year cardiac events in Mediterranean patients with non-ST elevation acute coronary syndrome. Atherosclerosis. 2010; 209(1): 300-5.
19. Abdel-Qadir HM, Chugh S, Lee DS. Improving prognosis estimation in patients with heart failure and the cardiorenal syndrome. Int J Nephrol. 2011; 2011: 351672.