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Serum uric acid on admission predicts in-hospital mortality in patients with acute coronary syndrome

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ABSTRACT

Background: Despite the association between uric acid and cardiovascular disease has been known for decades, the prognostic value of serum uric acid (UA) in all clinical manifestations of acute coronary syndrome (ACS), namely ST-elevation myocardial infarction (STEMI), NSTEMI and unstable angina, has not been definitively assessed.
Methods: This retrospective analysis included patients from previous SPAI and FAMI studies with the aim to investigate the association between serum uric acid and major adverse cardiovascular events at 180 days from hospital admission.
Results: 1548 patients were considered and divided in four groups, according UA concentration. Uricemia was significantly associated with gender, BMI, arterial hypertension, HDL-cholesterol, triglycerides, metabolic syndrome and glomerular filtration rate in univariate analysis. Multivariate logistic regression indicated that UA >6.0 mg/dL on admission increased the risk of in-hospital mortality in overall population (OR 2.9, 95%CI 1.4–6.1; $p = 0.0057$) and in patients with *de novo* ACS (OR 3.2, 95%CI 1.5–6.8; $p = 0.0033$). Comparable results were also obtained after adjusting the model for age, gender, body mass index, glomerular filtration rate, metabolic syndrome, acute revascularization and ethnicity. A positive correlation was observed between UA and C reactive protein concentrations in in-hospital deaths only (rho 0.41, $p = 0.027$).
Conclusion: In patients with acute coronary syndrome, uricemia levels above the current international reference limit (6.0 mg/dl) were associated with in-hospital mortality, independently from ethnicity and renal function.

1. Introduction

Acute coronary syndrome (ACS), a major clinical manifestation of atherothrombosis, refers to a wide spectrum of clinical presentations including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina [1]. Emerging evidence indicates that plaque phenotype, coronary blood flow, endothelial dysfunction, microvascular dysfunction and inflammation are pivotal mechanisms contributing to the onset of ACS [2]. Uric acid seems to be involved in many of these processes, thus contributing to atherosclerosis, plaque composition and vascular instability [3–6]. Furthermore, uric acid may be an independent risk factor for both cardiovascular disease [7–10] and kidney disease [10–11] and elevated levels of uric acid predict the development of arterial hypertension [10, 12], obesity [13] and diabetes [14]. However, it is still controversial whether uric acid is an independent predictor of cardiovascular disease [15]. A recent retrospective study has demonstrated that elevated levels of uric acid are an independent predictor of 1-year mortality in patients with ACS treated with percutaneous coronary intervention in a single site [16].

The aim of this study was to investigate the prognostic role of serum uric acid (UA) on admission during a middle term follow up of 180 days after hospital admission in a multi-ethnic international cohort of patients with the entire spectrum of ACS.

2. Material and methods

2.1. Study design

This retrospective analysis included patients with ACS who participated at the Stratificazione Prognostica Angina Instabile (SPAI) [17] and First Acute Myocardial Infarction (FAMI) [18] studies with available blood samples collected on admission, and appropriately stored for the measurement of UA concentration. The SPAI study was conducted

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from December 1997 to December 2001 and included patients with Braunwald class IIIB unstable angina diagnosed in presence of: (1) ischaemic ECG changes during recurrent chest pain; (2) evidence of myocardial ischaemia during exercise ECG stress test or during exercise radionuclide studies or pharmacological echocardiographic stress tests (with either dipyridamole or dobutamine); and (3) documentation of obstructive (> 50%) stenosis in at least one major epicardial artery during coronary angiography [17]. Patients were subsequently defined as NSTEMI and unstable angina according to high-sensitivity troponin levels. The FAMI study was conducted from October 2002 to April 2007 and involved patients who had electrocardiographic evidence of STEMI, no previous history of coronary artery disease and reported symptom onset of <6 h [18].

Patients who received allopurinol therapy, those with LVEF < 30% (STEMI) and LVEF < 40% (NSTEMI) and undergoing urgent CABG were excluded from the current analysis. Patients were followed by phone interview or clinical examination after 3 and 6 months from discharge to evaluate clinical outcomes and therapies. Information about death was obtained from hospital records, death certificates, or phone contact with relatives of the patient or the referring physician. Written informed consent was obtained from all patients. The studies were carried out in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee (SPAI Study was approved by Ethics Committee of Università Cattolica del Sacro Cuore, Rome; approval date 22/09/1997; FAMI Study was approved by Ethics Committee of Ospedale San Raffaele, Milan; approval date 8/11/2001).

2.2. Clinical evaluation

Each patient enrolled in the SPAI and FAMI studies underwent a physical examinations and standard ECG. Reference blood pressure was measured during the stable phase, after recovery from the acute phase or immediately before discharge. Information about demographic factors, socioeconomic factors (income, employment, level of education), lifestyle (physical activity during leisure and work time, dietary habits), psychosocial factors, and personal and family history of cardiovascular disease and traditional risk factors (smoking, diabetes, dyslipidaemia, hypertension) was collected in a structured standardized questionnaire [17,18]. Height, weight, and abdominal circumference were determined. Previous history of CHD, peripheral vascular disease and chronic renal disease were also recorded.

Non-fasting blood samples were obtained immediately upon admission. Blood was centrifuged, and serum and plasma samples were bar-coded and frozen at −80 °C until assayed at a core laboratory. Lipids were measured with standard, automated laboratory methods and serum C reactive protein was assayed by a high-sensitivity nephelometric method (Nephelometric 100 Analyzer; Behring, Scoppito, Italy).

In the present study, for each patient with available blood samples stored in a dedicated biological bank, serum creatinine and serum uric (UA) acid were measured in a central laboratory (Clinical Laboratory Service, IRCCS Ospedale San Raffaele, Milano), in a single batch, by personnel unaware of patients' characteristics. UA concentrations were determined with standard, automated laboratory methods with an enzymatic colorimetric test on a Cobas C 6000 (Roche Diagnostics, Monza Italy); the coefficient of variation was 2%, measured. Renal function was assessed through serum creatinine determination and estimated glomerular filtration rate (eGFR) was obtained using the four-component Modified Diet Renal Disease (MDRD) formula.

3. Statistical analysis

Continuous variables were reported as mean and standard deviation or median and interquartile range according to their distribution; comparison between groups were performed with ANOVA test and 2-sided Student's *t*-test or Wilcoxon test and Kruskal-Wallis test, as appropriate. Categorical variables were reported as percentage and compared with chi-square test. A p value < 0.05 was considered statistically significant.

Univariate correlation was obtained with a Spearman Rank-Order Correlation: Multivariate logistic regression models were used to assess the relationship between UA and outcomes. Estimates of odds ratios with their 95% confidence intervals were reported.

The study population was divided in four groups, *per* UA concentration. UA quartiles were: quartile 1 ≤ 4.2 mg/dl; quartile 2: 4.3 to 5.1 mg/dl; quartile 3: 5.2 to 6.0 and quartile 4 > 6.0 mg/dl. The primary endpoint was mortality at 180 days from hospital admission; the number of major adverse cardiac events (MACEs) occurring within 180 days was assessed; MACEs included death, heart failure, non-fatal stroke, non-fatal STEMI. Recurrence of acute coronary syndrome (both STEMI and NSTEMI) was also evaluated.

Premature ACS was defined as ACS in men aged ≤55 years and women aged ≤65 years, following the criteria of premature ischemic heart disease as applied to the definition of the family history for ischemic heart disease.

All statistical analysis and graphics were produced with JMP software (version 11.0.0, SAS Institute Inc., Cary, North Carolina, USA).

4. Results

A total of 1548 patients with ACS from SPAI and FAMI studies were included in the analysis. The UA concentrations ranged from 1.4 to 11.9 mg/dl and the population was divided in 4 quartiles according to the 25th percentile (4.2 mg/dl), median (5.1 mg/dl), and 75th percentile (6.0 mg/dl).

Baseline characteristics of each quartile group are listed in Table 1. Supplementary Table 1 reports also pharmacological treatment at discharged. The proportion of patients with NSTEMI/UA and STEMI was similar among groups; *de novo* ACS and premature ACS also occurred with similar frequency. No statistically significant differences were observed in UA distribution between European and Chinese patients (Table 1).

The prevalence of men, patients with arterial hypertension and metabolic syndrome tended to be significantly higher with the increasing quartiles of UA. BMI, Framingham Risk Score, triglycerides and serum creatinine showed a graded increase, whereas HDL-cholesterol and eGFR decreased according to the UA quartile.

In-hospital deaths and MACEs were assessed in the overall population and patients suffering from *de novo* ACS. In both settings, a higher proportion of in-hospital deaths was observed in quartile 4 while MACEs frequencies were similar across groups (Table 2).

Considering UA as a categorical variable (cut off: 6.0 mg/dl, quartile 4), UA >6.0 mg/dL increased the risk of in-hospital mortality in both overall population (OR 2.9, 95% CI 1.4–6.1, $p = 0.0057$) and *de novo* ACS (OR 3.2, 95%CI 1.5–6.8, $p = 0.0033$). Multivariate logistic regression analysis showed that the adjusted model for age, gender, eGFR classes, and metabolic syndrome (Model 1), obtained similar results (Overall population: OR 2.8, 95% CI 1.2–6.5, $p = 0.0143$; *de novo* ACS: OR 3.1, 95% CI 1.3–7.4, $p = 0.0095$). In addition to the variables considered in the Model 1, two further variables were evaluated: revascularization (Model 2) and revascularization and ethnicity (Model 3). In Model 2, in the overall population OR was 2.8 (95% CI 1.2–6.4, $p = 0.0187$), while in patients with *de novo* ACS OR was 3.0 (95% CI 1.3–7.4, $p = 0.016$); in Model 3, in overall population OR was 2.7 (95%CI 1.2–6.3, $p = 0.0226$) and in patients with *de novo* ACS OR was 3.0 (95%CI 1.3–7.3, $p = 0.0127$) (Table 3).

Furthermore, the correlation between UA and C-reactive protein (CRP) levels was assessed in patients who survived at the follow up, in patients who died during hospitalization and after hospital discharge. UA and CRP concentrations positively correlated in in-hospital dead patients (rho 0.42, $p = 0.038$) only, whilst the correlation between UA and CRP concentration was not observed in both survived patients and in patients who died after discharge (Fig. 1).

5. Discussion

The present study describes the relationship among UA, cardiovascular risk factors and outcome in a wide cohort of patients with ACS. First, UA was significantly associated with other well-established risk factors for cardiovascular disease, namely arterial hypertension, BMI, HDL-cholesterol, triglycerides, the main component metabolic syndrome and renal function. The role of UA as independent cardiovascular risk factor is still controversial. For decades, it has been described that uric acid was implicated in cardiovascular disease [7–10,15,19,20]. However, even if UA *per se* might not represent a modifiable direct risk factor for cardiovascular disease, it may be considered a predictive marker for cardiovascular risk that can worsen other established risk factors. In fact, evidence indicates that uric acid plays a role in hypertension, obesity, and diabetes [10–14].

Second, our study showed that elevated UA concentrations (>6.0 mg/dl) on admission were associated with an increased risk of