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Hyperuricemia as a prognostic factor after acute coronary syndrome

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ABSTRACT

Background and aims: Many studies have reported the independent association between uric acid and cardiovascular disease, its role as a risk predictor for outcomes in people with acute coronary syndrome remains controversial. This study aims to assess the association between hyperuricemia and medium/long-term clinical outcomes in people with acute coronary syndrome and determine whether adding hyperuricemia to the GRACE score improves its predictive capability.

Methods: This cohort study included patients admitted for acute coronary syndrome between 2008 and 2013. Outcomes were cardiovascular and total mortality, and major cardiovascular events. We used a multivariate model to adjust for potential confounding covariates and presented event rates with Kaplan-Meier curves. After adding hyperuricemia to the GRACE score, we compared scores from the reclassification table and the net reclassification improvement.

Results: 1119 participants were included and followed-up for a mean of 36 months. Multivariate models showed hyperuricemia was independently associated with higher cardiovascular mortality (HR:1.91; 95% CI:1.32−2.76; $p < 0.01$), higher all-cause mortality (HR:1.59; 95% CI:1.18−2.15; $p < 0.01$) and higher major cardiovascular event rates (HR:1.36; 95% CI:1.11−1.67; $p < 0.01$). The hyperuricemia addition to GRACE score led to reclassifying 26% of the participants, and net reclassification improvement was 34%. However, the area under the curve increase was 0.009 and not statistically significant ($p > 0.05$).

Conclusions: Hyperuricemia is associated with higher medium/long-term mortality and major cardiovascular event rates in patients following acute coronary syndrome. The addition of hyperuricemia to the GRACE score seems to improve risk classification but the discrimination of the new predictive model did not change. Hyperuricemic patients had higher all-cause mortality in medium and high-risk score categories.

1. Introduction

Different authors have suspected an association between elevated serum uric acid (SUA) levels and cardiovascular disease since the late nineteenth century [1,2]. A number of studies have shown that SUA concentration is significantly associated with cardiovascular conditions [3–7]. At the same time, elevated SUA levels are linked to various cardiovascular risk factors, including hypertension [8], dyslipidemia [9], diabetes [10], obesity [11], metabolic syndrome, kidney failure [12] and specific target organ damage, making it difficult to determine whether uric acid is a cause or a consequence of these conditions [13,14].

Many epidemiological studies have shown through multivariate analyses that hyperuricemia is an independent risk factor for the development of cardiovascular disease and/or vascular morbidity and mortality, particularly in patients with hypertension or

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congestive heart failure [15,16]. A recent systematic review showed that hyperuricemia may slightly increase the risk of CAD events, independently of traditional cardiovascular risk factors [17]. Nevertheless, not all population-based epidemiological studies support this hypothesis [18], and other authors have suggested that hyperuricemia is a risk marker rather than an independent risk factor [19,20]. Medical societies have not recognized elevated SUA as a cardiovascular risk factor [14].

The association between elevated SUA and poor clinical outcomes in people with stable CAD and heart failure is well documented [17,21], but less is known about SUA as a potential predictor of outcomes after acute myocardial infarction, particularly in high-risk patients [22,23]. Over the past few years, several studies have explored the value of on-admission SUA to predict outcomes in patients with acute coronary syndromes (ACS) [5,23]. A recent meta-analysis showed that hyperuricemia was associated with a 46% increased risk of adverse clinical events after any percutaneous coronary intervention (PCI) [24]. There is less evidence on how hyperuricemia impacts the long-term prognosis after ACS.

Acute myocardial infarction remains one of the most prevalent causes of death worldwide, with the highest mortality rates within the first month of an event [25]. Clinical decision-making requires an accurate assessment of cardiovascular risk, which has a significant influence on choosing between different management strategies that vary in terms of benefits, risks, and costs [26]. SUA may be a powerful tool to help stratify risk for cardiovascular disease [16], and risk stratification systems for patients with acute myocardial infarction, like the Global Registry of Acute Coronary Events (GRACE) [27], could benefit from including SUA, particularly as this marker is readily and reliably obtainable at a low cost [28].

Despite extensive research, the role of SUA as a potential risk predictor for outcomes in people with ACS remains controversial. Therefore, the present study aims to assess the prognostic value of hyperuricemia in ACS patients for medium/long-term clinical outcomes after hospital discharge and to evaluate the reclassification of the GRACE risk score.

2. Patients and methods

This is a prospective cohort study in a tertiary university hospital with a 24 h a day, seven days per week primary percutaneous coronary intervention service. We initiated a continuous registry of all non-scheduled admissions in the Cardiology Unit in December 2008 [29], and we included all consecutive patients admitted for an ACS between December 2008 and December 2013. ACS diagnosis was defined as [1] typical clinical symptoms of chest pain [2]; electrocardiographic changes indicative of myocardial ischemia/lesion; and/or [3] elevation of serum markers of myocardial damage. ACS was classified as ST-segment elevation ACS or non ST-segment elevation ACS based on electrocardiographic findings [30]. We excluded patients who died within 24 h of admission and those from whom we could not obtain SUA determination. All participants provided informed consent. The study was approved by the institutional review board and was carried out in accordance with the Helsinki Declaration.

After discharge, participant follow-up was carried out by means of outpatient visits, telephone calls, and revision of clinical reports and electronic medical records, in order to obtain clinical status and outcome events from study inclusion to October 2016 or first observed outcome event. All primary care visits, medical interventions, emergency calls, visits to the emergency room and hospital readmissions were recorded in a centralized electronic medical record system.

The primary endpoint was cardiovascular mortality. The secondary endpoints were all-cause mortality and major cardiovascular event (defined as non-fatal ACS, unplanned revascularization, or readmission for any cardiovascular disease including heart failure, stroke or unstable angina). Long-term survival analysis was performed only with patients discharged from hospital. Therefore, hospital mortality was not included as an endpoint.

At baseline, we collected demographic characteristics, cardiovascular risk factors, previous medical history, laboratory data during the hospitalization, vital signs on admission, treatment, and diagnosis at discharge from all patients.

SUA levels were routinely measured following overnight fasting from peripheral venous blood samples within the first 24–48 h of hospitalization. Colorimetry and uricase method were used to measure it. According to the local laboratory reference range, hyperuricemia was defined as SUA higher than 7 mg/dL (420 μmol/L) in men and 5.7 mg/dL (342 μmol/L) in women. The glomerular filtration rate (GFR) was estimated on admission from serum creatinine values with the Modification of Diet in Renal Disease (MDRD) study equation [31]. GFR values less than 60 mL/min/m^2 were considered to indicate kidney failure. We also obtained other routine biochemical measurements after overnight fasting: hemoglobin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and glycated hemoglobin A1C (HbA1c). We measured body weight and height during hospitalization and calculated body mass index (BMI).

We defined comorbid hypertension, dyslipidemia and diabetes mellitus according to previous diagnosis on patient medical reports or if the patient was receiving specific therapies. Participants with HbA1c greater than or equal to 6.5% and no previous diagnosis were codified as diabetics. We considered participants to have had previous CAD if they had been diagnosed with myocardial infarction, stable or unstable angina, or angina-driven coronary revascularization. Previous heart failure was codified in participants with at least one prior hospitalization plus these principal diagnoses recorded at discharge, as well as in those with typical signs and symptoms of heart failure, confirmed by echocardiogram. Patients underwent an echocardiography within 48 h post-admission, and left ventricular ejection fraction (LVEF) was calculated using the Simpson's method. Heart failure during hospitalization was defined as Killip class II or higher.

Risk stratification was performed by means of the GRACE score [27], with any score over 140 denoting high risk. Comorbidity was assessed by the Charlson index adapted for people with CAD [32].

In addition, we also collected medical complications and clinical events that occurred during hospital stay. We considered the following to be major hospital complications: cardiac arrest, heart failure, non-scheduled revascularization, stroke, major bleeding, blood transfusion and cardiogenic shock. A cardiologist was responsible for all diagnoses and medical histories, and all clinical variables were recorded at hospital discharge.

2.1. Statistical analysis

Data were processed with SPSS 22.0 and STATA 14.0 software. We present quantitative variables as means (standard deviation [SD]) and assess differences by the Student's *t*-test and ANOVA procedure. Qualitative variables are expressed as percentages, and differences were analyzed by Chi-square test. Event rates through follow-up are presented by Kaplan-Meier curves, and the survival distributions were compared by log-rank tests. Cox's hazard regression models were used for survival analyses once proportional risk tests were verified. Multivariate analysis was adjusted using the likelihood ratio test for variables selection procedure. A selective stepwise-all variables with a p value < 0.05 were assessed