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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

in a step-backward model. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI). The model's discriminative accuracy was assessed by the Harrell's C-statistic, while its calibration was tested by the Gronnesby and Borgan test, which is a model check for the Cox regression model using martingale residual processes grouped after the risk score. Additionally, we used the Cox's hazard regression model for survival analysis of subgroups stratified by the presence of diabetes, hypertension or kidney failure, including the same variables.

To assess reclassification measures, we applied methods suggested by Cook et al. [33] and Pencina et al. [34], comparing the additional value of hyperuricemia to the GRACE score. Reclassification tables were constructed to determine the numbers of participants who were reclassified by the model that included both scores. We then calculated the number and proportion of correctly reclassified participants based on the actual mortality rate observed in each GRACE strata through follow-up (<10%, 10–25% and >25%). The improvement in model performance was assessed by the continuous version of net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). Net reclassification improvement (NRI) represents the average weighted improvement in discrimination, and no censored data were allowed for its calculation. The area under the curve (AUC) and Hosmer-Lemeshow goodness-of-fit test were also calculated both for the models with and without the hyperuricemia data. With the Hosmer–Lemeshow test, the quality of the original and new model was compared. The threshold for establishing statistical significance was $p < 0.05$.

3. Results

The study population included 1323 patients, 204 of whom were excluded due to lack of SUA determination during hospital stay. Thus, the study cohort consisted of 1119 participants (74% men, n = 830) with a mean age of 68 (SD 13) years. Baseline characteristics are presented in Table 1. The prevalence of hyperuricemia was 34.4%; participants with high SUA levels were slightly older; had higher prevalence of hypertension, previous heart failure and kidney failure; and were more likely to be taking diuretics. Global assessment of comorbidities, assessed by the Charlson index, was also slightly higher in participants with hyperuricemia. The GRACE score was higher in the hyperuricemia group, with proportionally more participants classified as high risk compared to the group without hyperuricemia. Overall, the revascularization rate was 86.5%, but this was significantly lower in patients with hyperuricemia. With regard to the recommended treatment at discharge (Supplemental Table 1), the covariances between all treatments at discharge and hyperuricemia were considered and hyperuricemic participants were more likely to receive treatments in line with clinical practice guidelines, such as dual antiplatelet treatment, beta-blockers, angiotensin-converter enzyme inhibitors, angiotensin receptor blockers or statins. The use of allopurinol was very low in both groups.

Post-discharge follow-up was achieved for 98% of the patients, with a median follow-up of 36 months (interquartile range [IQR] 14.0 to 60.0). In our overall population, in-hospital mortality was 2.8%, but it was almost three-fold higher in participants with hyperuricemia (4.7% *vs.* 1.8%; $p = 0.005$). The incidence of major hospital complications was 8.7%, and this was also higher in participants with hyperuricemia (11.7% *vs.* 7.1%; $p = 0.009$). Overall, cardiovascular mortality rate was 10.9%; all-cause mortality, 16.3%; and major cardiovascular events, 36.9%. As shown in Fig. 1, participants with hyperuricemia had higher event rates, and survival curves diverged significantly very early after hospital discharge.

In the univariate analysis, age, sex, cardiovascular risk factors (BMI, hypertension, smoking habit, diabetes and dyslipidemia), previous coronary heart disease, stroke or heart failure, revascularization during hospitalization, GRACE score, Charlson index, medical treatment at discharge and hyperuricemia were significant predictors of outcome. The multivariate analysis, adjusted for age, sex, cardiovascular risk factors (BMI, hypertension, smoking habit, diabetes and dyslipidemia), glomerular filtration rate, previous coronary heart disease, heart failure or stroke, as well as medical treatments at discharge (clopidogrel, prasugrel, ticagrelor, dual antiplatelet treatment, betablockers, ACEI/ARB, statins, diuretics, espironolactone/eplerenone, nitrates, oral antidiabetics), showed that hyperuricemia was independently associated with higher cardiovascular and all-cause mortality as well as the combined endpoint of major cardiovascular events (Table 2). The model had a good discriminative power (Harrel's C-statistic = 0.81) and was accurately calibrated (Gronnesby and Borgan test = 0.77). We further explored the association of hyperuricemia with total and cardiovascular mortality by participant subgroups (see Table 1, Tables 2 and 3 in Ref [35]). In the subgroup of patients without kidney failure, both total and cardiovascular mortality were still significantly higher in hyperuricemic participants. However, in the group of non-diabetic participants, hyperuricemia was not a significant predictor of mortality. And for non-hypertensive patients, hyperuricemia was only a significant predictor of cardiovascular mortality.

Finally, we analyzed the results of adding hyperuricemia to the GRACE score (Table 3). When we performed the risk reclassification for all-cause mortality based on hyperuricemia using the original GRACE score (Supplemental Fig. 1), participants with hyperuricemia had higher mortality in medium and high risk score categories. The addition of hyperuricemia to the GRACE score led to reclassifying 26.1% (n = 284) of the participants (Table 3), and was associated with a continuous NRI of 0.343 (95% CI: 0.174 to 0.509), an event NRI of −0.040 (95% CI: −0.194 to 0.121), a non-event NRI of 0.382 (95% CI: 0.331 to 0.448), and an IDI of 0.012 (95% CI: 0.001 to 0.032). Both the original GRACE score and GRACE score with hyperuricemia remained calibrated within the reclassification table (reclassification Hosmer-Lemeshow chi-square 7.94 ($p = 0.439$) and 2.81 ($p = 0.945$) respectively). The AUC of the new model showed a slightly increase from 0.7065 to 0.7152 although without significant difference ($p > 0.05$).

4. Discussion

The prevalence of hyperuricemia was 34.4% in our ACS participants, and a SUA level above the normal range was independently associated with both total and cardiovascular mortality as well as major cardiovascular events in medium/long-term follow-up. The association of hyperuricemia with mortality remained significant in patients without kidney failure, but not in participants without diabetes. Moreover, the addition of hyperuricemia information to the GRACE risk score seemed to improve classification for a net of 38% of individuals without events. Although the new model had good calibration and discrimination, the increase in AUC was weak and not statistically significant.

The prevalence of hyperuricemia varies in different populations and areas [36]. The prevalence found in our study is similar to that reported by Timoteo et al. [37] in a Portuguese cohort. In contrast, the prevalence of hyperuricemia is lower in other countries [38,39]. Previous studies have also reported differences related to sex in prevalence and association with CAD [17]. However, we did not observe differences between men and women.

Participants with hyperuricemia in our study cohort had significantly higher prevalence of hypertension, kidney failure, previous heart failure, and diuretic treatment was significantly

Table 1
Baseline characteristics of the study population according to the presence of hyperuricemia.

Variable	Total	Hyperuricemia		*p*-value
		No	Yes	
N	1119	734 (65.6%)	385 (34.4%)	
Age, mean (SD)	68.1 (12.9)	67.1 (12.6)	70.0 (13.2)	<0.01
Males, n (%)	830 (74.2)	558 (76.1)	272 (70.6)	0.05
BMI (kg/m^2), mean (SD)	27.8 (4.4)	27.5 (4.3)	28.3 (4.7)	0.01
Hypertension, n (%)	751 (67.1)	469(63.9)	282 (73.2)	<0.01
Current smokers, n (%)	342 (30.6)	235(32.0)	107 (27.8)	0.14
Diabetes, n (%)	390 (34.9)	245 (33.4)	145 (37.7)	0.15
Dyslipidemia, n (%)	577 (51.6)	373 (50.8)	204 (53.0)	0.49
ST-elevation ACS, n (%)	351 (31.4)	232 (31.6)	119 (30.9)	0.81
Previous CHD, n (%)	324 (29.0)	215 (29.3)	109 (28.3)	0.73
Previous HF, n (%)	33 (2.9)	15 (2.0)	18 (4.7)	0.01
Previous stroke, n (%)	71 (6.3)	44 (6.0)	27 (7.0)	0.51
Peripheral arterial disease, n (%)	71 (6.3)	45 (6.1)	26 (6.8)	0.68
COPD, n (%)	101 (9.0)	61 (8.3)	40 (10.4)	0.25
Diuretic treatment before admission, n (%)	177 (15.8)	94 (12.8)	83 (21.6)	<0.01
Maxim Killip class >1, n (%)	200 (17.9)	92 (12.5)	108 (28.1)	<0.01
Charlson score, mean (SD)	2.3 (2.1)	2.3 (2.1)	2.5 (2.2)	0.04
Charlson score >4, n (%)	226 (20.2)	142 (19.3)	84 (21.8)	0.33
GRACE score, mean (SD)	136.7 (39.5)	132.1 (37.5)	145.4 (41.8)	<0.01
GRACE score >140, n (%)	470 (42.0)	273 (37.2)	197 (51.3)	<0.01
Revascularization, n (%)	968 (86.5)	650 (88.6)	318 (82.6)	<0.01
LVEF, mean (%)	55.4 (11.7)	56.7 (11.9)	52.8 (12.9)	<0.01
LVEF <35%, n (%)	105 (9.9)	52 (7.4)	53 (14.7)	<0.01
Uric acid (mg/dl), mean (SD)	5.9 (1.8)	5.0 (1.1)	7.7 (1.6)	<0.01
Hemoglobin (g/dl), mean (SD)	13.4 (5.3)	13.6 (6.4)	13.1 (2.2)	0.10
Total cholesterol total (mg/dl), mean (SD)	160.0 (45.2)	158.5 (41.6)	162.8 (51.4)	0.13
HDLc (mg/dl), mean (SD)	39.5 (23.3)	39.2 (13.8)	40.2 (34.9)	0.48
Triglycerides (mg/dl), mean (SD)	135.5 (74.4)	132.1 (77.4)	141.9 (68.0)	0.04
LDLc (mg/dl), mean (SD)	93.1 (37.2)	91.3 (35.4)	96.5 (40.3)	0.03
HbA1c (%), mean (SD)	6.5 (1.4)	6.5 (1.4)	6.5 (1.4)	0.81
Creatinine (mg/dl), mean (SD)	1.4 (6.5)	1.4 (8.0)	1.2 (0.5)	0.66
GFR <60 mL/min/1.72 m^2, n (%)	260 (23.2)	102 (13.8)	158 (41.1)	<0.01
GFR (ml/min/1.72m^2), mean (SD)	77.8 (28.2)	83.8 (26.0)	66.5 (28.8)	<0.01

ACS: acute coronary syndrome; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; HF: heart failure; LVEF: left ventricle ejection fraction; GFR: glomerular filtration rate; HbA1c: glycated haemoglobin; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol.

more frequent. The relationship of these factors with an elevated SUA level has been reported in other studies [40,41]. In relation to treatment with allopurinol, existing guidelines agree that urate-lowering therapy is not indicated for asymptomatic hyperuricemia in the absence of clinical gout [42]. We found a very low rate with no significant differences between groups, so we could not assess the influence of this drug on prognosis. Revascularization rates were higher in participants without hyperuricemia, but we believe that the higher prevalence of comorbidities and advanced age could have a negative influence on revascularization rates and the choice to perform other invasive procedures. The higher comorbidity in hyperuricemic patients might justify the difference in treatment at discharge between groups.

Although SUA levels are influenced by many factors [28], our results are consistent with previous studies [4,25,26,43,44], which have shown a significant relationship between SUA levels and poor clinical outcomes, adjusting for multiple potential confounders like cardiovascular risk factors. However, other authors state that SUA might not have a causal role in cardiovascular disease but rather simply indicate the presence of risk factors such as diabetes, hypertension or kidney failure [20]. This controversy has spurred the performance of different studies in populations with diabetes, hypertension and kidney failure, with conflicting results [16,45–49]. The subgroup analysis of our study demonstrated that the independent association between hyperuricemia and total and cardiovascular mortality was still significant in participants with GFR $\geq$60 mL/min/1.73 m^2, but not in participants without diabetes. For non-hypertensive patients, the association was only significant for cardiovascular mortality. These findings are consistent with studies showing that hyperuricemia might reflect an underlying insulin-resistance state, which works alone to raise cardiovascular risk [45]. However, the present study focus on the strength the hyperuricemia as a prognostic marker and future investigations should analyse populations without other risk factors.

Kaplan-Meier survival curves illustrate that patients with hyperuricemia had higher all-cause mortality in medium and high risk score categories. The addition of hyperuricemia to the GRACE risk score allowed to reclassify 26% of patients into different category and provided 34% net reclassification improvement. Event and non-event NRI measures considered separately persons who have and who do not have events. Among events, the hyperuricemia introduced more errors than corrections (NRI < 0). However, since there are more non-events than events (a common situation), the risk model containing SUA introduced far more corrections than errors overall. Hence, these results suggested that the addition of hyperuricemia improves prediction for non-events. In addition, the new model had good calibration and discrimination but the AUC increased only 0.009 without significant difference between original and new models. However, promising new markers have failed to produce large increases in the area under the curve [34]. Our results agree with Timoteo et al. [37], who found that the inclusion of SUA to GRACE score suggested effective reclassification (NRI = 44%) and better identification of those who do not have events than those who do despite the slight increase in AUC (from 0.78 to 0.79, $p = 0.350$). Levantesi et al. [26] also found that cardiovascular models containing SUA as a predictive factor performed better and the increase of AUC after adding SUA to GRACE score was 0.005 ($p = 0.0041$). Further validation in large prospective

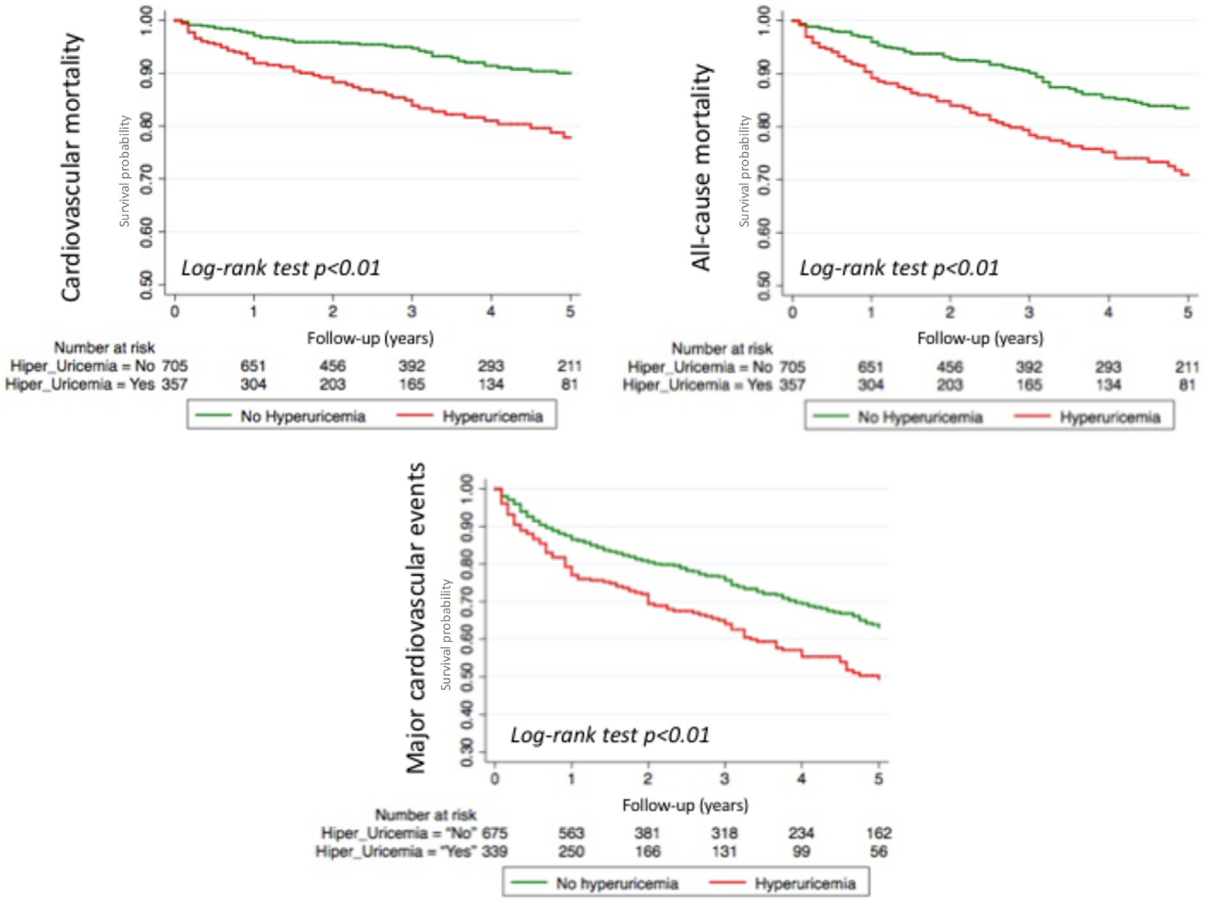

Fig. 1. Kaplan-Meier survival curves for cardiovascular mortality, all-cause mortality and major cardiovascular events, according to the presence of hiperuricemia.

Table 2
Multivariable Cox proportional hazard regression model (independent predictors of outcome).

Independent variables	HR (95% CI); *p*-value		
	Cardiovascular mortality	All-cause mortality	Major cardiovascular event
Age >75	2.87 (1.88–4.39); $p < 0.01$	2.46 (1.74–3.47); $p < 0.01$	1.75 (1.40–2.20); $p < 0.01$
Diabetes	1.67 (1.16–2.40); $p < 0.01$	1.40 (1.00–1.95); $p = 0.05$	1.35 (1.08–1.69); $p < 0.01$
Previous HF	2.57 (1.35–4.87); $p < 0.01$	2.49 (1.44–4.30); $p < 0.01$	1.37 (1.11–1.81); $p = 0.01$
Previous CHD	1.57 (1.08–2.28); $p = 0.02$	1.66 (1.22–2.27); $p < 0.01$	1.31 (1.06–1.62); $p < 0.01$
Hyperuricemia	1.91 (1.32–2.76); $p < 0.01$	1.59 (1.18–2.15); $p < 0.01$	1.36 (1.11–1.67); $p < 0.01$
Revascularization	0.27 (0.18–0.40); $p < 0.01$	0.39 (0.28–0.56); $p < 0.01$	0.54 (0.42–0.70); $p < 0.01$
Statins	0.58 (0.34–0.99); $p = 0.05$	0.43 (0.28–0.67); $p < 0.01$	0.61 (0.43–0.85); $p < 0.01$

Goodness-of-fit indicators: LRT = 169.2, $p < 0.001$.
HR: hazard ratio; CI: confidence interval; CHD: coronary heart disease; HF: heart failure.
Adjusted for age, sex, cardiovascular risk factors (BMI, hypertension, smoking habit, diabetes and dyslipidemia), glomerular filtration rate, previous coronary heart disease, heart failure or stroke, as well as medical treatments at discharge (clopidogrel, prasugrel, ticagrelor, dual antiplatelet treatment, betablockers, ACEI/ARB, statins, diuretics, espironolactone/eplerenone, nitrates, oral antidiabetics).

multicentre registries is needed to justify the addition of SUA in an enhanced GRACE score.

This is a prospective real-world study and there were several potential limitations to this study. First, this is a single-centre study and may have been subject to selection bias. However, since clinical features and outcomes are similar to other reports [50], we believe that our results are representative of daily clinical practice. Second, patients were classified according to uric acid levels obtained within the first 24–48 h of hospitalization, which could have been affected by the stress induced by the ACS; nonetheless, there is no evidence related to uric acid level variations related to an acute coronary event. Third, we excluded 15.4% of the patients due to patient'death or premature hospital discharge which avoided the uric acid level determination, and this could have resulted in excluding the highest risk patients that died before blood samples could be obtained. Fourth, the results were observed in a Spanish cohort with ACS and might not be generalizable to other populations. Fifth, there are differences in confounding factors between the groups, so any differences in outcome may be caused by the exposure itself, by differences in the measured and unmeasured confounders, or by both. Multivariate regression was used to lessen the bias caused by measured confounders, although it cannot adjust for unmeasured confounders. Sixth, statistical methods pertaining to net reclassification indices are not yet well-developed

Table 3
Reclassification table comparing all-cause mortality for risk model based on the GRACE risk score with and without hyperuricemia.

Model without hyperuricemia	Model with hyperuricemia			Total	Reclassification to newer category		
Estimated risk	<10%	10-25%	>25%		Lower	Higher	Total
<10%							
At risk (n)	213	64	0	277	0	64	64
Observed mortality(%)	6.69	12.27	0	7.98			
10–25%							
At risk (n)	115	481	59	655	115	59	174
Observed mortality (%)	9.13	15.78	28.04	15.72			
>25%							
At risk (n)	0	46	109	155	46	0	46
Observed mortality (%)	0	22.21	38.07	33.36			
Total							
At risk (n)	328	591	168	1087	161	123	284
Observed mortality (%)	7.55	15.90	34.54	16.26			

and for that reason we assessed the discrimination and calibration of risk models. However, further research in assessment methods of added usefulness of new markers with small prediction increment is needed. Seventh, although we found that the prevalence of hyperuricemia was not significant different between men and women, the studied association might be different according to the sex. Thus, data analysis stratified by sex with similar sample sizes should be performed in the future.

Regarding to the mechanism responsible for the relationship between SUA and cardiovascular outcomes, it remains unknown and this question can only be addressed through randomized clinical trials. Despite this fact, our data show that SUA determination may be a useful tool to help stratify risk for poor medium/long-term outcomes in patients following ACS. Moreover, SUA levels are routinely collected in clinical practice and can be obtained at a low cost.

In conclusion, hyperuricemia is independently associated with medium/long-term mortality and major cardiovascular events in ACS patients. Including hyperuricemia as a factor in the GRACE risk score led to reclassification of mortality risk in 26% of our participants, yielding a net reclassification improvement of 34%. Hence, hyperuricemia might be considered as an independent prognostic factor in ACS patients.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

AC, VBM and AL contributed to the design and implementation of the research, AC, VBM and AL contributed to acquisition of data, AC and AL performed the statistical analysis and drafted the manuscript. All authors discussed the results and contributed to the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.01.017.

References

[1] F.A. Mohamed, On Bright's disease, and its essential symptoms, Lancet 1 (1879) 399–401.
[2] A. Haig, On uric acid and arterial tension, BMJ 1 (1889) 288–291.
[3] M. Kanbay, M. Segal, B. Afsar, D.H. Kang, B. Rodriguez-Iturbe, R.J. Johnson, The role of uric acid in the pathogenesis of human cardiovascular disease, Heart 99 (2013) 759–766.
.
[4] F. Braga, S. Pasqualetti, S. Ferraro, M. Panteghini, Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis, Clin. Chem. Lab. Med. 54 (1) (2016 Jan) 7–15.
[5] L. Yan, Z. Liu, C. Zhang, Uric acid as a predictor of in-hospital mortality in acute myocardial infarction: a meta-analysis, Cell Biochem. Biophys. 70 (3) (2014 Dec) 1597–1601.
[6] C. Bickel, H.J. Rupprecht, S. Blankenberg, et al., Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease, Am. J. Cardiol. 89 (1) (2002 Jan 1) 12–17.
[7] L.K. Niskanen, D.E. Laaksonen, K. Nyyssönen, et al., Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study, Arch. Intern. Med. 164 (14) (2004 Jul 26) 1546–1551.
[8] J.P. Forman, H. Choi, G.C. Curhan, Plasma uric acid level and risk for incident hypertension among men, J. Am. Soc. Nephrol. 18 (1) (2007 Jan) 287–292.
.
[9] T.C. Peng, C.C. Wang, T.W. Kao, et al., Relationship between hyperuricemia and lipid profiles in US adults, BioMed Res. Int. 2015 (2015) 127596.
[10] N. Katsiki, N. Papanas, V.A. Fonseca, E. Maltezos, D.P. Mikhailidis, Uric acid and diabetes: is there a link? Curr. Pharmaceut. Des. 19 (27) (2013) 4930–4937.
[11] K. Masuo, H. Kawaguchi, H. Mikami, T. Ogihara, M.L. Tuck, Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation, Hypertension 42 (4) (2003 Oct) 474–480.
.
[12] Z. Soltani, K. Rasheed, D.R. Kapusta, E. Reisin, Potential role of uric acid in metabolic syndrome, hypertension, kidney injury, and cardiovascular diseases: is it time for reappraisal? Curr. Hypertens. Rep. 15 (3) (2013 Jun) 175–181.
[13] S. Shetty, A.H. Rao, A.K. Sampath Kumar, S. Rama Prakasha, Serum uric acid as a prognostic biomarker and its correlation with Killip class in acute myocardial infarction, Int. J. Biomed. Res. 04 (07) (2013).
[14] D.I. Feig, D.H. Kang, R.J. Johnson, Uric acid and cardiovascular risk, N. Engl. J. Med. 359 (17) (2008 Oct 23) 1811–1821.
[15] J.M. Pascual Izuel, Uricemia and metabolic syndrome in patients with arterial hypertension, Rev. Clin. Esp. 212 (9) (2012 Oct) 440–441.
[16] M. Alderman, K.J. Aiyer, Uric acid: role in cardiovascular disease and effects of losartan, Curr. Med. Res. Opin. 20 (3) (2004 Mar) 369–379.
[17] S.Y. Kim, J.P. Guevara, K.M. Kim, H.K. Choi, D.F. Heitjan, D.A. Albert,

Hyperuricemia and coronary heart disease: a systematic review and meta-analysis, Arthritis Care Res. 62 (2) (2010 Feb) 170–180.
[18] C. Lazzeri, S. Valente, M. Chiostri, C. Picariello, G.F. Gensini, Uric acid in the early risk stratification of ST-elevation myocardial infarction, Intern Emerg Med 7 (2012) 33–39.
[19] E.M. Antman, M. Hand, P.W. Armstrong, et al., 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction, J. Am. Coll. Cardiol. 51 (2) (2008 Jan 15) 210–247.
[20] B.F. Culleton, M.G. Lansom, W.B. Kannel, D. Levy, Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study, Ann. Intern. Med. 131 (1) (1999 Jul 6) 7–13.
[21] T. Niizeki, Y. Takeishi, T. Arimoto, et al., Hyperuricemia associated with high cardiac event rates in the elderly with chronic heart failure, J. Cardiol. 47 (5) (2006 May) 219–228.
[22] T.G. von Lueder, N. Girerd, D. Atar, et al., High-Risk Myocardial Infarction Database Initiative Investigators. Serum uric acid is associated with mortality and heart failure hospitalizations in patients with complicated myocardial infarction:findings from the High-Risk Myocardial Infarction Database Initiative, Eur. J. Heart Fail. 17 (11) (2015 Nov) 1144–1151.
[23] V. Trkulja, S. Car, On-admission serum uric acid predicts outcomes after acute myocardial infarction: systematic review and meta-analysis of prognostic studies, Croat. Med. J. 53 (2) (2012 Apr) 162–172.
[24] A.H. Wu, J.D. Gladden, M. Ahmed, A. Ahmed, G. Filippatos, Relation of serum uric acid to cardiovascular disease, Int. J. Cardiol. 213 (2016 Jun 15) 4–7.
[25] E. Gazi, A. Temiz, B. Altun, et al., The association between serum uric acid level and heart failure and mortality in the early period of ST-elevation acute myocardial infarction, Turk Kardiyol Dern Ars 42 (6) (2014 Sep) 501–508.
[26] G. Levantesi, R.M. Marfisi, M.G. Franzosi, et al., Uric acid: a cardiovascular risk factor in patients with recent myocardial infarction, Int. J. Cardiol. 167 (1) (2013 Jul 15) 262–269.
[27] C.B. Granger, R.J. Goldberg, O. Dabbous, et al., Predictors of hospital mortality in the global registry of acute coronary events, Arch. Intern. Med. 163 (2003) 2345–2353.
[28] S. Car, V. Trkulja, Higher serum uric acid on admission is associated with higher short-term mortality and poorer long-term survival after myocardial infarction: retrospective prognostic study, Croat. Med. J. 50 (6) (2009 Dec) 559–566.
[29] A. Cordero, V. Bertomeu-Gonzalez, J. Moreno-Arribas, et al., Burden of systemic hypertension in patients admitted to cardiology hospitalization units, Am. J. Cardiol. 108 (11) (2011) 1570–1575.
[30] E.A. Amsterdam, N.K. Wenger, R.G. Brindis, et al., 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American college of cardiology/American heart association task force on practice guidelines, J. Am. Coll. Cardiol. 64 (24) (2014) 139–228.
[31] National Kidney Foundation, K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification, Am. J. Kidney Dis. 39 (2 Suppl1) (2002 Feb). S1-266.
[32] M. Sachdev, J.L. Sun, A.A. Tsiatis, C.L. Nelson, D.B. Mark, J.G. Jollis, The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease, J. Am. Coll. Cardiol. 43 (4) (2004) 576–582.
[33] N.R. Cook, P.M. Ridker, Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures, Ann. Intern. Med. 150 (11) (2009) 795–802.
[34] M.J. Pencina, R.B. D'Agostino Sr., R.B. D'Agostino Jr., R.S. Vasan, Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond, Stat. Med. 27 (2) (2008 Jan 30), 157-72; discussion 207–212.
[35] A. Lopez-Pineda, A. Cordero, C. Carratala-Munuera; D. Orozco-Beltran, JA. Quesada; V. Bertomeu-Gonzalez; VF. Gil-Guillen; V. Bertomeu-Martinez. Association analysis between hyperuricemia and long term mortality after acute coronary syndrome in three subgroups of patients. Data in Brief [submitting].
[36] B. L, T. W, H.N. Z, et al., The prevalence of hyperuricemia in China: a meta-analysis, BMC Publ. Health 11 (2011 Oct 27) 832.
[37] A.T. Timóteo, A. Lousinha, J. Labandeiro, et al., Serum uric acid: a forgotten prognostic marker in acute coronary syndromes? Eur Heart J Acute Cardiovasc Care 2 (1) (2013 Mar) 44–52.
[38] E.W. Campion, R.J. Glynn, L.O. DeLabry, Asymptomatic hyperuricemia. Risks and consequences in the normative aging study, Am. J. Med. 82 (3) (1987 Mar) 421–426.
[39] S.A.-A. Abdurhman, Hyperuricemia in Saudi Arabia, Rheumatol. Int. (2001) 61–64.
[40] G. Ndrepepa, S. Braun, H.U. Haase, et al., Prognostic value of uric acid in patients with acute coronary syndromes, Am. J. Cardiol. 109 (9) (2012 May 1) 1260–1265.
[41] Y. Shacham, A. Gal-Oz, N. Flint, G. Keren, Y. Arbel, Serum Uric Acid Levels and Renal Impairment Among ST-segment elevation myocardial infarction patients undergoing primary percutaneous intervention, Cardiorenal Med 6 (3) (2016 May) 191–197.
[42] K.M. Jordan, J.S. Cameron, M. Snaith, et al., British society for rheumatology and British health professionals in rheumatology guideline for the management of gout, Rheumatology 46 (2007) 1372–1374.
[43] A.D. Liese, A.D. Liese, H.W. Hense, et al., Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. world health Organization Monitoring trends and determinants in cardiovascular diseases, Epidemiology 10 (4) (1999 Jul) 391–397.
[44] M.G. Kaya, H. Uyarel, M. Akpek, et al., Prognostic value of uric acid in patients with ST-elevated myocardial infarction undergoing primary coronary intervention, Am. J. Cardiol. 109 (2012) 486–491.
[45] F. Panero, G. Gruden, M. Perotto, et al., Uric acid is not an independent predictor of cardiovascular mortality in type 2 diabetes: a population-based study, Atherosclerosis 221 (1) (2012 Mar) 183–188.
[46] G. Zoppini, G. Targher, C. Negri, et al., Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients, Diabetes Care 32 (2009) 1716–1720.
[47] C. Lazzeri, S. Valente, M. Chiostri, V. Spini, P. Angelotti, G.F. Gensini, Uric acid and mild renal impairment in patients with ST-elevation myocardial infarction, Scand. Cardiovasc. J. 49 (1) (2015 Feb) 14–19.
[48] J. Kowalczyk, P. Francuz, R. Swoboda, et al., Prognostic significance of hyperuricemia in patients with different types of renal dysfunction and acute myocardial infarction treated with percutaneous coronary intervention, Nephron Clin. Pract. 116 (2010) 114–122.
[49] M.H. Alderman, H. Cohen, S. Madhavan, S. Kivlighn, Serum uric acid and cardiovascular events in successfully treated hypertensive patients, Hypertension 34 (1) (1999) 144–150.
.
[50] J.A. Barrabes, A. Bardaji, J. Jimenez-Candil, et al., Prognosis and management of acute coronary syndrome in Spain in 2012: the DIOCLES Study, Rev. Esp. Cardiol. 68 (2) (2015 Feb) 98–106.