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Uric acid in the early risk stratification of ST-elevation myocardial infarction

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Abstract Controversy still exists about uric acid as a potential prognosticrisk factor for outcomes in patients with acute myocardial infarction. We prospectively assessed, in 856 patients with ST-elevation myocardial infarction (STMI) consecutively admitted to our Intensive Cardiac Care Unit after primary percutaneous coronary intervention (PCI) whether uric acid (UA) levels are associated with in-hospital mortality and complications. Killip classes III--IV were more frequent in the 3° UA tertile that was associated with the highest values of peak Tn I ($p = 0.005$), NT-proBNP ($p < 0.001$), and fibrinogen ($p = 0.036$). Uric acid was associated with mortality (crude OR: 1.24; 95% CI 1.03–1.51; $p = 0.025$), but, when adjusted for Tn I and renal failure (as inferred by eGFR <60 ml/min/1.73 m^2), uric acid lost its statistical significance, while Tn I (100 pg/ml step OR: 1.002; 95% CI 1.000–1.003; $p = 0.007$) and renal failure (OR 9.16; 95% CI 3.60–23.32; $p < 0.001$) were independent predictors for in-ICCU mortality. Uric acid remained as independent predictor for in-ICCU complications (1 mg/dl step OR: 1.11; 95% CI 1.01–1.21; $p = 0.030$) together with admission glycemia (1 g/dl step OR: 1.50; 95% CI 1.19–1.91; $p < 0.001$) and renal failure (OR: 1.46; 95% CI 0.99–2.16; $p < 0.001$). In STEMI patients submitted to PCI, increased uric acid levels identify a subgroup more prone to in-ICCU complications, probably because hyperuricemia stems from several complex mechanisms ranging from pre-existing risk factors to the degree of myocardial ischemia (as indicated by Killip class, ejection fraction) and to the acute metabolic response (as inferred by glucose levels). Hyperuricemia is not independently associated with early mortality when adjusted for renal function and the degree of myocardial damage.

Keywords Uric acid · Risk stratification · ST-elevation myocardial infarction · Percutaneous coronary intervention

Introduction

In humans, uric acid (UA) is the end product of purine catabolism [1]. Its serum levels, governed by the production (liver) and elimination (mainly the kidney) rates, are influenced by several variables, such as genetically determined factors (i.e., activity of synthesizing enzymes or renal transport systems), racial and demographic characteristics (i.e., gender), and morbidity (i.e., renal failure, malignancies) [2].

The role of UA in cardiovascular and renal disease has been intensively investigated, although not without controversy [3, 4]. Over recent years, there has been renewed debate concerning the nature of the association between raised serum UA concentrations and cardiovascular disease (CVD), and controversy still exists on whether hyperuricemia is simply a risk marker (due to its strong association with cardiovascular risk factors), or an independent risk factor for atherosclerosis [5]. In general population samples at relatively low risk for CVD, UA is a very weak predictor of cardiovascular morbidity and mortality, once the effect of known con-founders is accounted for [6]. On the contrary, UA seems to be a significant independent predictor of CVD in certain categories of patients at high cardiovascular risk, such as diabetics [7], patients with stroke [8],

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heart failure [9], and angiographically proven coronary artery disease [10].

Less is known about UA as a potential prognosticrisk factor for outcomes in patients affected specifically by acute myocardial infarction [11–15], and several studies suggest that a higher UA is independently associated with poorer survival in these patients. However, studies on this topic differ in number size, time of UA measurement (early phase vs within the first 48 h), and type of reperfusion [thrombolysis vs. percutaneous coronary intervention (PCI)].

We prospectively assessed in 856 STEMI patients consecutively admitted to our Intensive Cardiac Care Unit (ICCU) after primary PCI, whether UA levels are associated with in-ICCU mortality and complications.

Methods

Study population

From 1st January 2005 to 31st December 2009, 856 consecutive patients with STEMI (within 12 h from symptoms' onset) were admitted to our Intensive Cardiac Care Unit (ICCU), which is located at a tertiary center.

In our hospital, in Florence, the reperfusion strategy of STEMI patients is represented by primary PCI [16–19]. Patients are first evaluated by the Medical Emergency System staff in the pre-hospital setting and then directly admitted to the catheterization laboratory or transferred to it after a rapid stabilization in the Emergency Department (ED). After primary PCI, they are admitted to our ICCU.

A successful procedure was defined as an infarct artery stenosis <20% associated with TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow. Failure PCI was defined as resulting in TIMI grade 0–2 flow, regardless of the degree of residual stenosis [16].

The diagnosis of STEMI was based on the criteria of the American College of Cardiology/American Heart Association [17].

On ICCU admission, after PCI, in a fasting blood sample the following parameters were measured: glucose (g/l), troponin I (ng/ml), uric acid (mg/dl) [14], NT-pro Brain Natriuretic Peptide (NT-BNP) (pg/ml) [14], leukocyte count ($\times 10^3$/µl), fibrinogen (mg/dl), erythrocyte sedimentation rate (ESR), glycated hemoglobin (%), cholesterol (mg/dl) and triglycerides (mg/dl). Creatinine (mg/dl) was also measured in order to calculate glomerular filtration rate (ml/min/1.73 m^2). Glucose values and Tn I were measured three times a day, and peak glucose and peak Tn I were considered [20], respectively.

Transthoracic two-dimensional echocardiography was performed on ICCU admission in order to measure left ventricular ejection fraction (LVEF).

In-ICCU mortality and in-ICCU complications were recorded. [21].

The study was approved by an appropriate ethics committee, and all patients gave informed consent to participate.

Statistical analysis

Data have been processed by means of SPSS 13.0 statistical package (SPSS Inc, Chicago, IL, USA). A p value <0.05 was considered statistically significant. Data are reported as frequencies (percentages) and medians [95% Confidence interval (CI)] and analyzed by means of χ^2 (or Fisher's exact text, when appropriate) and Mann–Whitney U test, respectively. Moreover, study population has been divided by tertiles of uric acid levels in order to investigate which variables differed between the three subgroups. Logistic regression analysis was carried out considering as outcomes intra-ICCU mortality and complications. In these two multivariable analyses, candidate variables were chosen as those that demonstrated significantly differences at univariable analysis or were clinically relevant. Backward procedure (probability for entry: 0.05; probability for removal: 0.10) was repeated until all variables in the model reached statistical significance.

Results

Table 1 depicts the clinical characteristics of the 856 consecutive STEMI patients included in the study. In more than half of the cases (54.2%) the acute myocardial infarction was anterior. The incidence of PCI failure was 5.4%. In-ICCU mortality rate was 3.3% (28/856) while in-ICCU complications were detected in the 28.0% (240/856).

Tertiles of uric acid (UA tertile) are shown in Table 2. STEMI patients in the third UA tertile were the oldest ($p < 0.001$) and showed the highest BMI ($p < 0.001$) and triglyceride values ($p < 0.001$) and the lowest eGFR ($p < 0.001$) and EF ($p < 0.001$). Killip classes III–IV were more frequent in the third UA tertile that was associated with the highest values of peak Tn I ($p = 0.005$), NT-proBNP ($p < 0.001$), and fibrinogen ($p = 0.036$). Admission glucose and peak glycemia showed a progressive significant increase among UA tertiles ($p = 0.006$ and $p < 0.001$, respectively). The incidence of in-ICCU complications was significantly higher in the third UA tertile while in-ICCU mortality rate did not show statistical differences among UA tertiles.

When evaluating UA values on the basis of gender-specific tertiles (Table 3), it was observed that in the first tertile men showed higher values of uric acid, while in the

Table 1 Clinical characteristics of patients with ST elevation myocardial infarction included in the study

	Median (25th–75th pct) or frequency (%)
Age (years)	67.0 (58–76)
Males/females	643/213 (75.1/24.9%)
History of	
Diabetes mellitus, n (%)	212 (24.8%)
Smoking, n (%)	537 (62.7%)
COPD, n (%)	73 (8.5%)
Previous PCI, n (%)	115 (13.4%)
Previous MI, n (%)	126 (14.7%)
Hypertension, n (%)	433 (50.6%)
Drugs on admission	
ACE-inhibitors	774 (90,4%)
ARB	17 (2%)
Diuretics	102 (11.9%)
Estimated GFR (ml/min/1.73 m^2)	78.4 (63.7–94.0)
AMI location	
Anterior, n (%)	464 (54.2%)
Inferior, n (%)	328 (38.3%)
Other, n (%)	64 (7.5%)
Coronary artery disease	
No disease, n (%)	2 (0.2%)
1-vessel, n (%)	331 (38.7%)
2-vessel, n (%)	297 (34.7%)
3-vessel, n (%)	226 (26.4%)
LM involvement, n (%)	63 (7.4%)
CABG involvement, n (%)	15 (1.8%)
PCI failure, n (%)	46 (5.4%)
Admission EF(%)	45.0 (35.0–50.0)
Latency (min)	240 (165–340)
In-hospital mortality, n (%)	28 (3.3%)
In-hospital complications, n (%)	240 (28.0%)

COPD chronic obstructive pulmonary disease, *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blockers, *PCI* percutaneous coronary intervention, *MI* myocardial infarction, *GFR* glomerular filtration rate, *AMI* acute myocardial infarction, *LN* left main coronary artery, *CABG* coronary artery bypass graft, *EF* ejection fraction

second and third tertiles no gender-related differences in uric acid values were observed.

Logistic regression analysis

Uric acid (considered as continuous variable) was associated with mortality (1 mg/dl step crude OR: 1.24; 95% CI 1.03–1.51; $p = 0.025$). When adjusted for Tn I and renal failure (as inferred by eGFR < 60 ml/min/1.73 m^2), uric acid lost its statistical significance (uric acid 1 mg/dl step: OR: 1.02; 95% CI 0.83–1.26; $p = 0.858$), while Tn I

(100 pg/ml step OR: 1.002; 95% CI 1.000–1.003; $p = 0.007$) and renal failure (OR 9.16; 95% CI 3.60–23.32; $p < 0.001$) were independent predictors for in-ICCU mortality: Hosmer–Lemershow goodness-of-fit $\chi^2 = 5.889$; $p = 0.660$ (Table 4).

Uric acid was associated with in-hospital complications (1 mg/dl step crude OR: 1.16; 95% CI 1.07–1.26; $p < 0.001$). At multivariable logistic regression analysis uric acid remained as an independent predictor for in-ICCU complications (1 mg/dl step OR: 1.11; 95% CI 1.01–1.21; $p = 0.030$) together with admission glycemia (1 g/dl step OR: 1.50; 95% CI 1.19–1.91; $p < 0.001$) and renal failure (OR: 1.46; 95% CI 0.99–2.16; $p < 0.001$): Hosmer–Lemershow goodness-of-fit $\chi^2 = 3.554$; $p = 0.895$.

Discussion

The present investigation describes an independent association between higher UA levels and in-ICCU complications in a large series of consecutive STEMI patients submitted to PCI.

Several factors may account for this finding. First, we confirm the strong association between UA levels and known cardiovascular risk factors, since UA values paralleled those of two of the components of the metabolic syndrome (that is BMI and triglycerides) [1, 5, 6]. Second, UA values appeared to be related to infarct size (as indicated by peak Tn I), hemodynamic derangement (as inferred by ejection fraction, Killip class and NT-proBNP) as well as to the metabolic and inflammatory acute responses to stress (as indicated by hyperglycemia and fibrinogen values). Overall it can be speculated that, in the early phase of STEMI patients, hyperuricemia stems from several complex mechanisms, ranging from pre-existing risk factors to the degree of myocardial ischemia, and to the acute metabolic response. The underlying mechanisms linking hyperuricemia to in-ICCU complications in the early phase of STEMI may be related to the pro-oxydant [22] and pro-inflammatory actions [23] attributed to uric acid and previously described in patients with overt ischemic conditions [24, 25]. In experimental models it is observed that, during tissue ischemia, the enzymatic effect of xantine oxidase is the production of reactive species of oxygen (ROS) and uric acid [25, 26]; hyperuricemia per se has been described to impair endothelium-dependent vasodilatation by reduction NO-synthase in animal experiments [27].

Previous studies investigated the relation between UA levels and mortality in patients with acute myocardial infarction, but the results are far from unanimous. Whereas Homayounfar et al. [12] report that hyperuricemia is not an independent prognostic risk factor for in-hospital death

Table 2 Tertiles of uric acid in the study population

		1° tertile (≤4.8 mg/dl; n = 211)	2° tertile (4.8–6.2 mg/dl; n = 225)	3° tertile (> 6.2 mg/dl; n = 207)	p value
Age (years)	Females	71.0 (61.0–78.0)	76.0 (62.0–82.0)	76.0 (68.0–82.0)	0.015
	Males	62.0 (55.0–72.0)	65.0 (55.5–74.0)	68.0 (59.0–76.0)	<0.001
	p	<0.001	<0.001	<0.001	
BMI	Females	24.0 (22.0–26.6)	25.4 (23.1–28.2)	26.0 (23.9–28.1)	0.007
	Males	25.6 (23.5–27.0)	26.3 (24.6–28.4)	26.5 (24.4–28.7)	<0.001
	p	0.004	0.082	0.446	
Estimated GFR (ml/min/1.73 m^2)	Females	75.0 (64.6–90.4)	71.8 (52.0–86.6)	56.0 (33.7–74.3)	<0.001
	Males	89.3 (77.1–104.3)	82.9 (71.3–95.9)	69.8 (49.7–86.2)	<0.001
	p	<0.001	<0.001	<0.001	
AMI anterior (%)	Females	49 (56.3%)	36 (60.0%)	39 (59.1%)	0.892
	Males	102 (48.6%)	116 (51.8%)	126 (58.5%)	0.028
	p				
Killip class					
I-II	Females	80 (91.9%)	53 (88.4%)	52 (78.6%)	0.054
	Males	201 (95.3%)	203 (90.2%)	187 (85.5%)	Females
III-IV	Females	7 (8.1%)	7 (11.7%)	14 (21.4%)	0.006
	Males	10 (4.7%)	22 (9.8%)	30 (14.5%)	Males
	p				
EF (%)	Females	45.0 (40.0–50.0)	40.0 (35.0–45.0)	40.0 (35.0–50.0)	0.007
	Males	45.0 (39.0–53.0)	45.0 (38.0–50.8)	42.0 (35.0–50.0)	0.001
	p	0.310	0.001	0.360	
PCI failure	Females (n = 213)	5 (5.7%)	7 (11.7%)	6 (9.1%)	0.436
	Males (n = 635)	10 (4.7%)	9 (3.9%)	9 (4.3%)	0.927
	p	0.774	0.051	0.211	
Glucose (g/l)	Females	1.38 (1.16–1.74)	1.47 (1.24–1.82)	1.52 (1.23–2.12)	0.073
	Males	1.24 (1.07–1.62)	1.26 (1.09–1.56)	1.34 (1.14–1.78)	0.024
	p	0.059	<0.001	0.017	
Peak glucose (g/l)	Females	1.60 (1.31–1.93)	1.73 (1.39–2.16)	2.04 (1.61–2.66)	<0.001
	Males	1.46 (1.24–1.86)	1.44 (1.22–1.78)	2.54 (1.32–2.08)	0.004
	p	0.092	<0.001	<0.001	
HbA1c (%)	Females	6.1 (5.6–6.5)	6.0 (5.7–6.3)	6.1 (5.7–6.9)	0.266
	Males	5.8 (5.5–6.5)	5.9 (5.6–6.3)	5.9 (5.6–6.4)	0.580
	p	0.176	0.711	0.015	
HbA1c > 6.5%	Females (n = 153)	13 (21.7%)	9 (21.4%) 31	17 (33.3%)	0.290
	Males (n = 415)	30 (23.3%)	(21.1%)	27 (19.4%)	0.745
	p	0.808	0.962	0.044	
Peak Tn I	Females	60.6 (36.0–117.0)	112.0 (43.5–216.9)	91.0 (32.5–292.2)	0.018
	Males	69.5 (32.9–143.4)	75.7 (39.1–168.5)	99.0 (33.1–208.0)	0.095
	p	0.397	0.175	0.516	
NT-proBNP	Females	1306 (590–3230)	3664 (1738–6535)	4689 (1802–12708)	<0.001
	Males	844 (324–1662)	1234 (434–2408)	1686 (618–4071)	0.002
	p	0.023	<0.001	<0.001	
Uric acid	Females	3.7 (3.2–4.2)	5.6 (5.3–5.8)	7.5 (6.7–8.5)	<0.001
	Males	4.2 (3.7–4.5)	5.6 (5.3–6.0)	7.3 (6.7–8.2)	<0.001
	p	<0.001	0.756	0.283	

Table 2 continued

		1° tertile (≤4.8 mg/dl; n = 211)	2° tertile (4.8–6.2 mg/dl; n = 225)	3° tertile (> 6.2 mg/dl; n = 207)	p value
ESR	Females	34 (20–46)	34 (22–50)	39 (18–56)	0.729
	Males	20 (12–36)	24 (14–38)	26 (12–47)	0.235
	p	<0.001	0.001	0.020	
Leucocytes (×10³/μl)	Females	10.2 (8.6–13.5)	12.5 (9.4–15.1)	11.0 (9.1–14.7)	0.076
	Males	11.0 (9.0–13.6)	10.7 (8.7–14.1)	11.2 (9.2–14.4)	0.480
	p	0.167	0.099	0.905	
CRP positivity	Females (n = 182)	37 (49.3%)	38 (71.7%)	36 (66.7%)	0.023
	Males (n = 528)	91 (54.8%)	100 (52.6%)	100 (58.1%)	0.572
	p	0.429	0.013	0.264	
Fibrinogen	Females	390 (354–470)	408 (344–493)	455 (354–521)	0.145
	Males	368 (320–445)	382 (328–450)	393 (319–527)	0.149
	p	0.015	0.118	0.055	
Total cholesterol	Females	198 (171–222)	187 (153–224)	185 (151–223)	0.610
	Males	180 (154–204)	188 (159–210)	184 (148–210)	0.372
	p	0.004	0.486	0.234	
HDL cholesterol	Females	46 (39–56)	46 (36–52)	42 (34–52)	0.091
	Males	41 (35–49)	39 (34–44)	40 (33–47)	0.113
	p	<0.001	0.004	0.038	
LDL cholesterol	Females	127 (106–152)	122 (90–154)	115 (88–150)	0.428
	Males	117 (96–140)	118 (98–144)	114 (92–140)	0.342
	p	0.035	0.611	0.606	
Triglycerides	Females	81 (62–106)	93 (70–135)	111 (82–146)	0.001
	Males	98 (68–130)	104 (82–145)	106 (81–147)	0.017
	p	0.024	0.134	0.938	
In-hospital complications	Females	26 (29.9%)	22 (37.3%)	25 (38.5%)	0.479
	Males	41 (19.5%)	60 (26.7%)	66 (32.3%)	0.013
	p	0.054	0.118	0.365	
In hospital mortality	Females	0	6 (10.0%)	5 (7.4%)	0.015
	Males	4 (1.9%)	6 (2.7%)	7 (3.4%)	0.639
	p	0.326	0.022	0.170	

Comparisons have been performed with χ^2 or Fisher's exact test for categorical variables and with Kruskal–Wallis (between tertiles of uric acid) and Mann–Whitney U (between gender) for continuous variables

BMI body mass index, *GFR* glomerular filtration rate, *AMI* acute myocardial infarction, *EF* ejection fraction, *PCI* percutaneous coronary intervention, *HbA1c* glycosilated hemoglobin, *Tn I* troponin I, *NT-proBNP* N terminal-pro brain natriuretic peptide, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HDL* high density lipoprotein, *LDL* low-density lipoprotein

Table 3 UA analyis on the basis of sex specific tertiles

		1°tertile (≤4.8 mg/dl; n = 211)	2° tertile (4.8–6.2 mg/dl; n = 225)	3° tertile (>6.2 mg/dl; n = 207)	p value
Uric acid	Females	3.7 (3.2–4.2)	5.6 (5.3–5.8)	7.5 (6.7–8.5)	<0.001
	Males	4.2 (3.7–4.5)	5.6 (5.3–6.0)	7.3 (6.7–8.2)	<0.001
	p	<0.001	0.756	0.283	

Comparisons have been performed with χ^2 or Fisher's exact test for categorical variables and with Kruskal–Wallis (between tertiles of uric acid) and Mann–Whitney U (between gender) for continuous variables

after AMI, Kojima et al. [13] find that the total mortality rate of patients whose serum UA concentrations are in the highest quartile is about 3.7 times higher than in those whose UA concentrations are in the lowest quartile. In their retrospective study (the Japanese Acute Coronary Syndrome Study), the Authors conclude that serum UA is a

Table 4 Multivariate and univariate analysis

	OR	95% CI	p	Hosmer–Lemeshow p
Univariate logistic regression analysis: outcome ICCU death				
eGFR < 60 ml/min/1.73 m^2	11.79	4.93–28.19	<0.001	0.326
TnI	1.26	1.11–1.43	<0.001	0.145
(100 pg/ml step)				
Uric acid	1.24	1.03–1.51	0.025	0.636
(1 mg/dl step)				
Multivariate logistic regression analysis: outcome ICCU death				
eGFR < 60 ml/min/1.73 m^2	9.16	3.60–23.32	<0.001	
TnI (100 pg/ml step)	1.18	1.04–1.33	0.008	
Uric acid (1 mg/dl step)	1.02	0.83–1.26	0.858	
Hosmer–Lemeshow χ^2 5.889, $p = 0.660$				
Univariate logistic regression analysis: outcome in-ICCU complications				
Uric acid (1 mg/dl step)	1.16	1.06–1.26	<0.001	0.076
TnI (100 pg/ml step)	1.10	1.02–1.19	0.010	0.785
Adm. glycemia (1 g/dl step)	1.72	1.37–2.15	<0.001	0.343
eGFR < 60 ml/min/1.73 m^2	2.05	1.46–2.88	<0.001	0.395
Multivariate logistic regression analysis: outcome in-ICCU complications				
Uric acid (1 mg/dl step)	1.11	1.01–1.21	0.030	
TnI (100 pg/ml step)	1.05	0.98–1.12	0.177	
Adm. glycemia (1 g/dl step)	1.50	1.19–1.91	<0.001	
eGFR < 60 ml/min/1.73 m^2	1.46	0.99–2.16	0.055	
Hosmer–Lemeshow χ^2 3.554, $p = 0.895$				

suitable marker for predicting AMI-related future. In their investigation, patients (admitted from January to December 2002) were enrolled within 48 h after onset of symptoms, and reperfusion was performed in 84% (mainly by means of mechanical reperfusion). Our group [14] recently documents in a homogeneous population of 466 STEMI patients all submitted to primary PCI within 12 h from symptoms' onset, that uric acid levels, measured after mechanical revascularization on ICCU admission, is an independent risk factor for in-hospital mortality. In the present investigation, performed in a larger cohort of STEMI patients, all submitted to mechanical revascularization, we failed to confirm the independent association between uric acid and in-ICCU mortality, since when uric acid was adjusted for eGFR and Tn I (that is renal function and the extension of myocardial damage, respectively) it was no longer associated with early mortality. Discrepancies between the two studies can be related principally to the different number of patients enrolled, since the studies were performed in comparable STEMI populations.

In conclusion, in STEMI patients submitted to PCI, increased uric acid levels identify a subgroup more prone to in-ICCU complications, probably because hyperuricemia stems from several complex mechanisms ranging from pre-existing risk factors to the degree of myocardial ischemia and to the acute metabolic response.

Hyperuricemia is not independently associated with early mortality when adjusted for renal function and the degree of myocardial damage.

Conflict of interest None.

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