The association between serum uric acid level and heart failure and mortality in the early period of ST-elevation acute myocardial infarction

ST yükselmeli akut miyokart enfarktüslü hastalarda ürik asit düzeyi ile erken dönem kalp yetersizliği ve mortalite arasındaki ilişki

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ABSTRACT

Objectives: Uric acid (UA) is a strong marker of cardiovascular disease. Therefore, we aimed to determine the relationship between serum UA levels and cardiovascular events in patients in the early period of their acute myocardial infarction.

Study design: This retrospective study included 586 consecutive patients with ST-elevated myocardial infarction (STEMI) who were admitted to the hospital between March 2010 and February 2012. The study population was divided into two groups; the first group included hyperuricemic patients (n=107; uric acid level >6 mg/dl in women and >7 mg/dl in men), and the second group included patients with normal UA level (n=479). Multivariate analysis was used to demonstrate the predictive value of UA levels in groups.

Results: Patients in the hyperuricemic group were older (median 66 years *vs.* 60 years, p=0.001), and the ratio of female patients was higher (35.5% *vs.* 16.9%, p=0.001). Patients with hyperuricemia had a significantly higher incidence of in-hospital cardiovascular mortality than the normal group (15.9% *vs.* 3.1%, p<0.001). Advanced heart failure (class ≥3) was more frequent among hyperuricemic patients (17.8% *vs.* 8.8%, p=0.006). Age ≥70 years, chest pain duration >6 hours and hyperuricemia (hazard ratio (HR): 1.83, 95% confidence interval: 1.02-3.27; p=0.041) were found to be independent predictors of advanced heart failure. Hyperuricemia was found to be an independent predictor of in-hospital cardiovascular mortality in multivariate analyses (HR: 5.32, 95% confidence interval: 2.46-11.49; p=0.001).

Conclusion: This study showed that a high serum UA level is an independent predictor of cardiovascular mortality and morbidity during the in-hospital period of STEMI.

ÖZET

Amaç: Ürik asit (ÜA) kalp damar hastalığı için güçlü bir belirteçtir. Bu çalışmada akut miyokart enfarktüsü geçiren hastalarda serum ÜA düzeyi ile kardiyovasküler olaylar arasındaki ilişkiyi araştırmayı amaçladık.

Çalışma planı: Koroner yoğun bakım ünitesinde Mart-2010 ile Şubat-2012 tarihleri arasında ST yükselmeli miyokart enfarktüsü (STYME) tanısı ile takip edilen 586 hasta, bu geriye dönük çalışmaya alındı. Başvuru sırasında bakılan ÜA düzeyine göre hastalar iki gruba ayrıldı. Hiperürisemik grup (n=107): ÜA düzeyi kadınlarda >6 mg/dl ve erkeklerde >7 mg/dl; normal grup (n=479): ÜA düzeyi belirtilen değerlerin altında olanlar. Hiperüriseminin kalp damar hastalığı mortalitesini öngörmedeki değeri çok-değişkenli analiz ile değerlendirildi.

Bulgular: Hiperürisemik grup normal grupla karşılaştırıldığında daha yaşlı (ortanca 66 yaş ve 60 yaş, p=0.001) ve kadın cinsiyet oranı daha fazlaydı (%35.5 ve %16.9, p=0.001). Hiperürisemi grubunda, normal gruba göre kalp damar hastalığına bağlı ölüm daha yüksek oranda görüldü (%15.9 ve %3.1, p<0.001). Kalp yetersizliği (sınıf ≥3) gelişme oranları da hiperürisemik grupta daha fazla bulundu (%17.8 ve %8.8, p=0.006). İleri yaş (≥70), altı saatten uzun süren göğüs ağrısı ve hiperürisemi (risk oranı: 1.83, %95 güven aralığı: 1.02-3.27, p=0.041) ileri kalp yetersizliği için bağımsız değişkenler olarak bulundu. Çok değişkenli analiz sonucunda hiperürisemi hastane içi mortalite için bağımsız öngördürücü olarak saptandı (risk oranı: 5.32; %95 güven aralığı: 2.46-11.49; p=0.001).

Sonuç: Bu çalışma serum ÜA yüksekliğinin STYME'li hastalarda hastane içi dönemde kalp damar hastalığı kökenli ölümler için bağımsız bir risk faktörü olduğunu göstermiştir.

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Previous studies have suggested that uric acid (UA) is associated with the development of cardiovascular diseases. UA levels are correlated with cardiovascular risk factors for atherosclerosis, such as older age, male sex, obesity, dyslipidemia, and insulin resistance.[1] Additionally, in some studies, UA was found to be an independent risk factor for both cardiovascular and renal diseases.[2-4] Furthermore, UA was found to be a strong marker of cardiovascular disease including acute and chronic heart disease, heart failure and stroke.[5-8]

Abbreviations:

AMI	*Acute myocardial infarction*
CI	*Confidence interval*
DM	*Diabetes mellitus*
GFR	*Glomerular filtration rate*
HF	*Heart failure*
HR	*Hazard ratio*
HT	*Hypertension*
STEMI	*ST-elevated AMI*
UA	*Uric acid*

Acute myocardial infarction (AMI) remains one of the most significant causes of death worldwide, and patients with AMI have a higher mortality rate during the first month following an event, especially during in-hospital stays.[9] Hence, in this study, we aimed to evaluate the relationship between serum UA levels and cardiovascular events and the incidence of mortality during in-hospital period in patients with ST-elevated acute myocardial infarction (STEMI).

PATIENTS AND METHODS

Patient population

The records of patients with AMI admitted to the coronary care unit from March 2010 to February 2012 were evaluated retrospectively. A total of 586 patients with STEMI (467 men and 119 women) were included in this study after excluding patients who had no UA measurements and who had to be sent to another cardiology center for rescue percutaneous transluminal coronary angioplasty (PTCA). A diagnosis of STEMI was defined as >30 minutes of continuous typical chest pain and ST-segment elevation ≥2 mm in two contiguous electrocardiography leads within 12 hours of symptom onset or within 18 hours if there was evidence of continuing ischemia or hemodynamic instability. The demographic information, cardiovascular history and risk factors (smoking, hypertension and diabetes mellitus) of patients were obtained from medical records. Hypertension (HT) was defined as use of antihypertensive drugs or baseline blood pressure exceeding 140/90 mmHg. Fasting blood sugar more than 126 mg/dl or the use of anti-diabetic medications were defined as diabetes mellitus (DM). The admission glomerular filtration rate (GFR) was estimated by the simplified Modification of Diet in Renal Disease (MDRD).[10] GFR <60 ml/min/m^2 was defined as renal failure. The study population was divided into normal and hyperuricemic groups according to baseline UA levels. Hyperuricemia was defined as a UA level >6 mg/dl in women and >7 mg/dl in men.[11,12] Advanced heart failure was defined as Killip classification ≥3 and cardiovascular death was defined as death due to AMI, heart failure or arrhythmia.

Analysis of serum UA levels and other laboratory data

Biochemical values were evaluated retrospectively from blood samples obtained by antecubital vein puncture upon admission to the emergency department. Serum UA levels of patients were measured with a Beckman Coulter Synchron LX20 device by uricase-peroxidase colorimetric method. Measurements of creatinine, total cholesterol, high-density cholesterol, low- density cholesterol, and triglyceride levels were studied by standard clinical chemistry techniques.

Statistical analysis

All statistical studies were carried out with the Statistical Package for the Social Sciences (SPSS) program (version 15.0, SPSS, Chicago, IL, USA). Quantitative variables were expressed as the median (interquartile range), and qualitative variables were expressed as percentages (%). All measurements were evaluated with the Kolmogorov-Smirnov test and were found to be non-normally distributed. A comparison of parametric values between the two groups was performed using the Mann-Whitney U-test. Categorical variables were compared by the chi-square or Fisher's exact test. Backward-stepwise multivariate logistic regression analysis was performed to identify independent predictors of in-hospital cardiovascular mortality, advanced heart failure (Killip ≥3) and any of these events. A p value <0.05 was considered statistically significant.

RESULTS

No significant difference was found between the groups regarding thrombolytic treatment during the in-hospital period, tobacco use, HT, DM, and local-

Table 1. Clinical data, risk factors, and treatments in patients

Variable	High UA level*(n=107)		Low UA level (n=479)		*p*
	%	n	%	n	
Age (years)	66	38-92	60	19-97	0.001
Female	35.5	38	16.9	81	0.001
Hypertension	26.2	28	29.7	142	0.466
Diabetes mellitus	42.1	45	38.6	185	0.511
Current smoker	32.1	34	36.7	176	0.365
Thrombolytic	59.8	64	68.3	327	0.093
LMWH	96.2	100	98.7	473	0.065
Acetyl salicylic acid	97.1	102	98.1	469	0.524
Clopidogrel	96.1	99	99.0	473	0.034
Beta-blocker	83.7	87	90.8	434	0.031
ACEI	77.1	81	85.2	408	0.043
Blood glucose, (mg/dl)	128 (56-508)		123 (58-520)		0.368
GFR (MDRD) (mL/min/m^2)	60 (19.6-111.1)		82.9 (5.8-240.1)		0.001
Myocardial infarction hour	5 (1-18)		4 (1-25)		0.427
Total cholesterol (mg/dl)	181 (88-285)		185 (74-348)		0.179
LDL (mg/dl)	117 (43-204)		123 (28-246)		0.045
HDL (mg/dl)	34 (16-58)		32 (13-71)		0.053
Triglyceride (mg/dl)	131 (44-516)		124 (21-887)		0.697
Uric acid (mg/dl)	7.6 (6.1-11.9)		5.2 (2.5-7)		0.001
Urea (mg/dl)	41.5 (14-102)		32 (13-93)		0.001
Creatinine (mg/dl)	1.2 (0.7-3.2)		0.9 (0.4-7.1)		0.001
In-hospital mortality	15.9	17	3.1	15	0.001
Advanced heart failure	17.8	19	8.8	42	0.006

*Hyperuricemia was defined as >6 mg/dL in men and >7 mg/dL in women. ACEI: Angiotensin converting enzyme inhibitor; ASA: Acetyl salicylic acid; GFR: Glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LMWH: Low molecular weight heparin; MDHD: Modification of diet in renal disease; MI: Myocardial infarction; n: Number of patients; UA: Uric acid.

ization of MI. Mean hospital stay was 6.7 days. Table 1 demonstrates the clinical characteristics of the groups. The patients in the hyperuricemic group were older (median 66 years *vs.* 60 years, p=0.001) and the ratio of female patients was higher (35.5% *vs.* 16.9%, p=0.001). Hyperuricemic patients had a significantly higher incidence of in-hospital cardiovascular mortality than the normal group (15.9% *vs.* 3.1%, p<0.001). Killip class ≥3 was more frequent in hyperuricemic patients (17.8% *vs.* 8.8%, p=0.006).

Patients with and without in-hospital mortality and/or heart failure were compared (Table 2). Patients with developing heart failure and/or in-hospital mortality were older (p=0.001) and had higher UA levels (p=0.006). Independent predictors of in-hospital cardiovascular mortality were determined by a backward-stepwise multivariate logistic regression (Table 3). Age ≥70 years, hyperuricemia, not receiving thrombolytic treatment, beta blocker, or angiotensin-converting enzyme inhibitor (ACEI), DM, GFR <60 mL/min/m^2, and female gender were associated with mortality in univariate analysis. Not receiving a beta blocker or thrombolytic treatment and hyperuricemia were found to be independent predictors of in-hospital cardiovascular mortality in multivariate analyses (hazard ratio [HR]: 5.32, 95% confidence interval: 2.46-11.49; p=0.001). In receiver operating characteristic (ROC) curve analysis, UA levels of 7 mg/dl

Table 2. Clinical data, risk factors and treatments in patients with and without heart failure and/or mortality

Variable	HF and/or exitus (+) (n=95)		HF and/or exitus (–) (n=491)		*p*
	%	n	%	n	
Age (years)	69	43-92	60	19-97	0.001
Female	35.8	34	17.3	85	0.001
Hypertension	31.6	30	28.6	140	0.555
Diabetes mellitus	50.5	48	37.1	182	0.014
Current smoke	30.5	29	36.9	181	0.233
Thrombolytic	45.3	43	70.9	348	0.001
LMWH	98.9	94	98.2	479	0.587
Acetyl salicylic acid	98.9	94	97.7	477	0.45
Clopidogrel	96.8	92	98.8	480	0.165
Beta-blocker	86.2	81	90.2	440	0.247
ACEI	83.2	79	83.8	410	0.868
Blood glucose (mg/dl)	137 (69-393)		122 (56-520)		0.001
GFR (MDRD) (ml/min/m^2)	73.0 (5.8-139.2)		80.9 (20.7-240.1)		0.001
Myocardial infarction hour	7 (1-24)		4 (1-25)		0.001
Total cholesterol (mg/dl)	176 (88-297)		185 (74-348)		0.085
LDL (mg/dl)	117 (43-212)		122 (28-246)		0.187
HDL (mg/dl)	33 (19-71)		32 (13-66)		0.118
Triglyceride (mg/dl)	108 (36-516)		129 (21-987)		0.008
Uric acid (mg/dl)	5.9 (2.6-11.9)		5.5 (2.6-11.2)		0.006
Urea (mg/dl)	37 (14-102)		32 (13-84)		0.002
Creatinine (mg/dl)	1.0 (0.6-7.1)		1.0 (0.4-3.2)		0.085
Anterior myocardial infarction	50.5	48	40.7	200	0.077

ACEI: Angiotensin converting enzyme inhibitor; ASA: Acetyl salicylic acid; GFR: Glomerular filtration rate; HDL: High-density lipoprotein; HF: Heart failure; LDL: Low-density lipoprotein; LMWH: Low molecular weight heparin; MDHD: Modification of diet in renal disease; MI: Myocardial infarction; n: Number of patients.

and 6 mg/dl were determined to be effective cut-off points in female and male patients with ST elevation for in-hospital mortality, with a sensitivity of 70% and a specificity of 90% (area under the curve=0.73, 95% confidence interval: 0.6-0.86; p=0.007) and with a sensitivity of 68% and a specificity of 68% (area under the curve=0.681, 95% confidence interval 0.52-0.83; p=0.007), respectively (Figure 1a, b).

Independent predictors of advanced heart failure were found as age ≥70 years, chest pain duration >6 hours and hyperuricemia (HR: 1.83, 95% confidence interval: 1.02-3.27; p=0.041) in multivariate analysis (Table 4). Hyperuricemia was also found to be an independent predictor of heart failure and/or in-hospital mortality (HR: 2.56, 95% confidence interval: 1.49-4.38; p=0.001). Table 5 shows other risk factors for heart failure and/or in-hospital mortality.

DISCUSSION

This study showed that UA levels are independently associated with in-hospital mortality and advanced heart failure in patients with STEMI. Our results extend previous findings by showing that hyperuricemia is a marker of in-hospital mortality in patients with STEMI.

Uric acid (UA) has long been known to be a cardiovascular risk factor. Clinical and epidemiological studies have shown that there is an association between high levels of UA and the severity of coro-

Table 3. Uni- and multi-variate analyses for risk factors of in-hospital cardiovascular mortality

Variable	Hazard ratio (95% CI)	*p*
Age ≥70 years	3.51 (1.70-7.24)	0.001
No thrombolytic treatment	4.88 (2.26-10.54)	0.001
Diabetes mellitus	1.58 (0.77-3.24)	0.204
Hyperuricemia	5.83 (2.81-12.12)	0.001
Chest pain time (>6 h)	3.35 (1.60-7.00)	0.001
Glomerular filtration rate (MDRD) (<60 ml/min)	2.72 (1.28-5.75)	0.009
Gender (Female)	0.34 (0.16-0.72)	0.005
No Beta-blocker treatment	3.74 (1.64-8.52)	0.002
No angiotensin converting enzyme inhibitor treatment	2.49 (1.14-5.46)	0.022
Anterior myocardial infarction	1.08 (0.51-2.29)	0.835
Backward-stepwise*		
No thrombolytic treatment	4.56 (2.06-10.12)	0.001
No beta-blocker treatment	2.89 (1.16-7.21)	0.023
Hyperuricemia	5.32 (2.46-11.49)	0.001

*Multivariate analysis: Age ≥70 years, no thrombolytic treatment, hyperuricemia, renal failure, female gender, chest pain time >6 hours, and not receiving ACEI and BB treatment were entered into the model. MDRD: Modification of diet in renal disease; CI: Confidence interval.

Table 4. Univariate and multivariate analyses for risk factors of in-hospital advanced heart failure (Killip ≥3)

Variable	Hazard ratio (95% CI)	*p*
Age (≥70 years)	2.61 (1.58-4.28)	<0.001
No thrombolytic treatment	2.19 (1.34-3.58)	<0.001
Diabetes mellitus	1.60 (0.98-2.61)	0.057
Hyperuricemia	2.08 (1.2-3.60)	0.009
Chest pain time (>6 h)	2.1 (1.48-3.95)	<0.001
Glomerular filtration rate (MDRD) (<60 ml/min)	1.98 (1.14-3.43)	0.014
Gender (Female)	2.38 (1.40-4.03)	0.001
No beta-blocker treatment	1.21 (0.57-2.58)	0.614
No angiotensin converting enzyme inhibitor treatment	0.87 (0.44-1.71)	0.688
Anterior myocardial infarction	0.72 (0.44-1.17)	0.189
Backward-stepwise*		
Gender (Female)	1.74 (0.99-3.06)	0.052
Age (≥70 years)	1.84 (1.08-3.16)	0.025
Hyperuricemia	1.83 (1.02-3.27)	0.041
Chest pain time (>6 h)	2.01 (1.19-3.39)	0.008

*Multivariate analysis: Age ≥70 years, no thrombolytic treatment, diabetes mellitus, hyperuricemia, renal failure, female gender, and chest pain time >6 hours were entered into the model. MDRD: Modification of diet in renal disease; HF: Heart failure, CI: Confidence interval, HR: Hazard ratio.

nary artery atherosclerosis.[13] Increased serum UA levels were independently and significantly associated with cardiovascular mortality over a long-term period. These findings suggest a relationship between

Table 5. Univariate and multivariate analyses for risk factors of in-hospital advanced heart failure (Killip ≥3) and/or exitus

Variable	Hazard ratio (95% CI)	*p*
Age (≥70 years)	3.12 (1.98-4.92)	<0.001
No thrombolytic treatment	2.82 (1.80-4.41)	<0.001
Diabetes mellitus	1.83 (1.11-2.69)	0.015
Hyperuricemia	2.81 (1.72-4.60)	<0.001
Chest pain time (>6 h)	2.84 (1.81-4.44)	<0.001
GFR (MDRD) (<60 ml/min)	2.06 (1.25-3.41)	0.005
Gender (Female)	2.66 (1.64-4.30)	<0.001
No beta-blocker treatment	1.47 (0.76-2.83)	0.249
No Angiotensin converting enzyme inhibitor treatment	1.05 (0.58-1.89)	0.868
Anterior myocardial infarction	1.48 (0.95-2.30)	0.078
Backward-stepwise*		
Age (≥70 years)	2.34 (1.39-3.81)	0.001
Chest pain time (>6 h)	2.25 (1.38-3.66)	0.001
Anterior myocardial infarction	1.67 (1.01-2.62)	0.044
Hyperuricemia	2.56 (1.49-4.38)	0.001

*Multivariate analysis: Age ≥70 years, no thrombolytic treatment, diabetes mellitus, hyperuricemia, renal failure, female gender, and anterior MI were entered into the model. . GFR: Glomerular filtration rate; MDRD: Modification of diet in renal disease; CI: Confidence interval.

high serum UA levels and coronary artery disease, although the underlying mechanisms remain unclear.[3] Several studies have shown a significant correlation between UA and atherosclerosis, inflammation, oxidative stress, and endothelial dysfunction.[14-17] UA is a product of purine metabolism that is produced by xanthine oxidase.[18] Xanthine oxidase activity and the production of UA causes the generation of oxygen free radicals and may be associated with the atherosclerotic process due to oxygen free radicals.[19,20] Additionally, Akpek et al.[21] reported that hyperuricemia is associated with endothelial dysfunction and microvascular disease in patients with STEMI, and they concluded that free radicals may be responsible for the

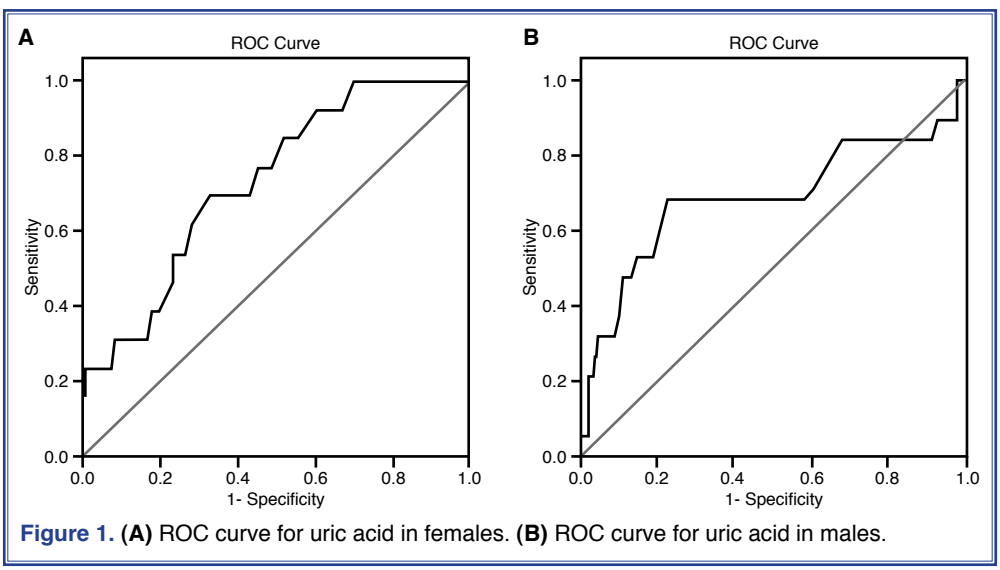

Figure 1. (A) ROC curve for uric acid in females. **(B)** ROC curve for uric acid in males.

no-reflow phenomenon during re-perfusion therapy. Furthermore, hyperuricemia may decrease nitric oxide production in vascular endothelium, which plays an important role in the regulation of coronary blood flow.[22,23] The success of re-perfusion therapy, either with thrombolytic or primary coronary intervention, for providing normal coronary flow is an important factor for preserving myocardial performance and decreasing mortality in AMI.[21,24] Kaya et al.[11] showed that elevated levels of UA are significantly related to lower thrombolysis in myocardial infarction (TIMI) flows in infarct- related artery and higher in-hospital and long-term adverse events in patients with STEMI who had undergone primary percutaneous coronary intervention (PCI). In this study, we found that hyperuricemia independently predicts mortality and is strongly associated with in-hospital cardiovascular events in patients with STEMI. No usage of thrombolytic therapy and beta blocker treatment was also associated with in-hospital mortality.

Recent studies showed that UA is related to the severity of heart failure after AMI.[25] Low cardiac output and tissue hypoxia can cause inadequate excretion of UA.[26] In our study, patients with higher UA levels had more frequent advanced heart failure (Killip 3 and 4), and GFR was lower than normal in the UA group. Older age and prolonged chest pain were found to be other independent predictors of advanced heart failure. Female gender was not statistically significant, but was closely related to the development of heart failure.

Hyperuricemia was associated with higher inflammatory activity and the severity of coronary atherosclerosis.[2,7] Older patients had a high inflammatory burden due to having comorbidities such as DM, renal failure and inflammation, which are important factors for ensuing myocardial damage.[26,27] Anterior MI localization was not independently related to in-hospital mortality nor advanced heart failure in our study, although the anterior localization was more frequent in the hyperuricemic group. These findings may be associated with inadequate reperfusion rather than the localization of the MI, and these results were in line with other studies.[11,25] On the other hand, the risk for severe heart failure and/or in-hospital mortality was independently associated with an anterior localization of AMI, older age, prolonged chest pain, and hyperuricemia. The results of this study suggest that patients with anterior MI, prolonged chest pain, older age, and hyperuricemia were at a higher risk for mortality and/or advanced severe heart failure during the in-hospital period and that these patients should be given intensive medical therapy and referred to a center where invasive treatment is available.

This study had a number of limitations. First, it is a retrospective study. Second, patient long-term survival and cardiac conditions could not be assessed because the patient records and coronary angiography results were not known. Another limitation is that most of the patients were male. Associations between inflammatory and oxidative stress markers were not evaluated. Lastly, successful thrombolytic treatment could be not evaluated in our study.

In conclusion, it is suggested that UA levels on admission strongly and independently predict cardiovascular mortality in patients with STEMI during the in-hospital period. Additionally, hyperuricemia is associated with advanced heart failure in these patients. The majority of deaths occur in the first hours of the in-hospital period of AMI. UA, a simple and inexpensive biomarker, can be used in risk stratification, and patients with STEMI with hyperuricemia should be monitored closely for cardiovascular events during the in-hospital period.

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