High serum uric acid levels may increase mortality and major adverse cardiovascular events in patients with acute myocardial infarction

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ABSTRACT

الأهداف: لتحديد صحة حمض اليوريك كعلامة نذير محتملة للنتائج طويلة المدى للمرضى الذين يعانون من احتشاء عضلة القلب الحاد AMI الذين يخضعون للتدخل التاجي عن طريق الجلد PCI.

الطريقة: أجريت مراجعة منهجية وتحليل تلوي واسترجعنا البيانات من دراسات متعرضه بأثر رجعي ومستقبلي والتي توضح فيما إذا كان مستوى حمض اليوريك في الدم يؤثر على تشخيص المرضى الذين يعانون من التهاب AMI.

النتائج: أُدرجت 13دراسة شملت 9371 مريضاً. أدى ارتفاع مستوى حمض اليوريك في الدم HSUA لزيادة معدل الوفيات المتوسطة أو طويلة الأجل (نسبة الخطر RR=2.32, 95% فترات الثقة CI 2.00–2.70) ومعدل وفيات أعلى قصير المدى (RR=3.09 CI: 95% 2.58–3.71) وارتفاع مخاطر القلب والأوعية الدموية الرئيسية المتوسطة أو طويلة الأجل MACE (RR=1.70, 95% CI: 1.54–1.88) ومعدل وفيات أعلى على المدى القصير (RR=2.47 95% CI: 2.08–2.92) لمرضى AMI. في مجموعة PCI الفرعية زاد مستوى HSUA من الوفيات متوسطة أو طويلة الأجل (RR=2.33, 95% CI: 1.89 to 2.87) و مخاطر MACE متوسطة أو طويلة الأجل (RR=1.64, 95% CI: 1.48–1.82) وارتفاع مخاطر MACE على المدى القصير (RR 2.43, 95% CI: 2.02–2.93) للمرضى الذين تم علاجهم مع PCI بعد AMI. في مجموعة PCI الفرعيه كان هناك معدل وفيات أعلى قصير المدى (RR=6.70, 95% CI: 3.14-14.31) في المجموعة التي لديها مستويات HSUA فاصله وكان معدل الوفاة أعلى من المجموعة التي لديها مستويات HSUA فاصله أعلى (RR=2.69, 95% CI: 2.09–3.46)

الخاتمة: زادت مستويات HSUA معدلات الوفاة و خطر MACE بشكل ملحوظ في مرضى AMI. وكان لارتفاع معدلات SUA (معدلات طبيعية) أثر ملحوظ على الوفيات على المدى القصير للمرضى الذين خضعوا إلى PCI ولم يحظوا بالاهتمام في الدراسات السابقة ومع ذلك، يتعين اجراء المزيد من الابحاث في هذا الشأن.

Objectives: To determine the validity of uric acid as a potential prognostic marker for long-term outcomes of patients with acute myocardial infarction (AMI) and those with AMI undergoing percutaneous coronary intervention (PCI).

Methods: Systematic review and meta-analysis were performed. We retrieved data from retrospective and prospective cohort studies that investigated whether serum uric acid (SUA) level affects the prognosis of patients with AMI.

Results: Thirteen studies involving 9371 patients were included. High serum uric acid (HSUA) level increased mid/long-term mortality (risk ratio (RR)=2.32, 95% confidence intervals (CI): 2.00–2.70) and had higher short-term mortality (RR=3.09, 95% CI: 2.58–3.71), higher mid/long-term major adverse cardiovascular events (MACE) risk (RR=1.70, 95% CI: 1.54–1.88), and higher short-term MACE risk (RR=2.47, 95% CI: 2.08–2.92) for patients with AMI. In the PCI subgroup, the HSUA level also increased mid/long-term mortality (RR=2.33, 95% CI: 1.89 to 2.87) and had higher mid/long-term MACE risk (RR=1.64, 95% CI: 1.48–1.82), and higher short-term MACE risk (RR 2.43, 95% CI: 2.02–2.93) for patients who were treated with PCI after AMI. Particularly in the PCI subgroup, a higher short-term mortality (RR=6.70, 95% CI: 3.14–14.31) was presented in the group with lower HSUA cut-off level, and the mortality was higher than the group with higher HSUA cut-off level (RR=2.69, 95% CI: 2.09–3.46).

Conclusion: The HSUA level significantly increased the mortality and MACE risk of patients with AMI. Mild elevation of SUA levels (normal range) have started to have a significant impact on the short-term mortality of patients who underwent PCI, and has not received the attention of previous studies. However, this condition should be further investigated.

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With the developments in antithrombotic and reperfusion therapies over the past several years, the mortality of acute myocardial infarction (AMI) has been steadily decreasing. However, coronary artery disease (CAD) is still the leading cause of death worldwide.[1] Uric acid is an end metabolite of purine.[2] Hyperuricemia is often accompanied by metabolic syndrome, such as hypertension, diabetes, dyslipidemia, and obesity, which are all known risk factors of coronary heart disease (CHD).[3] Cardiovascular health may suffer from the adverse effects caused by elevated serum uric acid (SUA) levels. The odds ratio (OR) for CHD was 2.59 for patients with UA levels >9 mg/dL.[4] The risk for many diseases was increased with an increased SUA level although the SUA level <7.0 mg/dL.[5] Many studies and two meta-analyses indicated an independent association between hyperuricemia and major adverse cardiovascular events (MACE) and mortality.[6,7] Although many researches were conducted on the link between hyperuricemia and cardiovascular disease, their causal relationship remains controversial;[8] Two meta-analyses have found that high serum uric acid (HSUA) level could significantly increase the mortality and risk of MACE in patients with AMI.[9,10] One of these 2 meta-analyses only analyzed in-hospital mortality. Hence, the effect of HSUA on the long-term prognosis of patients with AMI and those undergoing percutaneous coronary intervention (PCI) subsequently is not well known. To determine the validity of uric acid as a potential prognostic marker for long-term outcomes of patients with AMI and those undergoing PCI, we systematically reviewed published reports on uric acid and AMI to assess the prognostic value of SUA as a risk factor for increased mortality and MACE.

Methods. *Literature search.* We retrieved cohort studies (prospective and retrospective) regarding whether SUA level affected the prognosis of patients with AMI from the following databases: Embase, PubMed, Cochrane Library (up to May 17, 2016). Our search strategies included the following search terms, ("uric acid" OR "uricemia" OR hyperuricemia) AND ("myocardial infarction" OR "acute coronary syndrome" OR "MI" OR "ACS") AND ("mortality" OR "major adverse cardiovascular events" OR "MACE") (Just search human studies. Language was restrained as English). We referred to the Meta-analysis of Observational Studies in Epidemiology[11] as a reference when making the search strategy. In addition, we manually retrieved literatures to ensure identification of all published trials.

Study eligibility. Studies will be adopted if they fulfilled the criteria for inclusion as follows: (1) original, cohort studies of adult patients; (2) exposure factor, including hyperuricemia or HSUA level; (3) outcomes, including in-hospital mortality or short-term mortality (<30 days) or mid/long-term mortality (>6 months) or MACE; (4) sample size at least 100 cases; (5) score/star of study based on the Newcastle–Ottawa Scale (NOS)[12] more than 7. Three major elements in NOS were used to evaluate the cohort study: selection (0–4 stars), comparability (0–2 stars), and outcome (0–3 stars). The full star was nine. In addition, we excluded studies without specific detailed data. We selected the study with the longest follow-up time (FUT) if data were reported repeatedly over time.

Study selection. Two authors based on the study eligibility independently selected the studies. The first author performed the primary screening through the titles and abstracts. We obtained the full text if we cannot rule out this research through its title and abstracts. After the primary screening, the texts were independently screened by 2 reviewers. Any disparities were resolved through discussion and arbitration by a third reviewer.

Data extraction. Two researchers independently extracted data from each study. A third reviewer was included for arbitration purposes. We contacted the authors of the study that had incomplete or unclear data. The data extracted included the sample size, number of exposure or non-exposure group, gender, age, HSUA cut-off level, and whether a successful treatment option was provided, such as PCI, outcome, FUT, variable controlled, number of mortality or MACE, and the data needed in NOS.

Statistical analysis. The data accumulated were used to calculate the risk ratio (RR) and 95% confidence intervals (CI) of HSUA as a risk to affect the incidence rate of MACE and mortality (significance level, $p<0.05$). The random effects model (D+L) was used while considering the differences in the evaluated settings. We illustrated relevant baseline characteristics in the studies and used the chi-square test based on Cochran's Q test and I^2 statistics (significance level, $p<0.1$) to assess the

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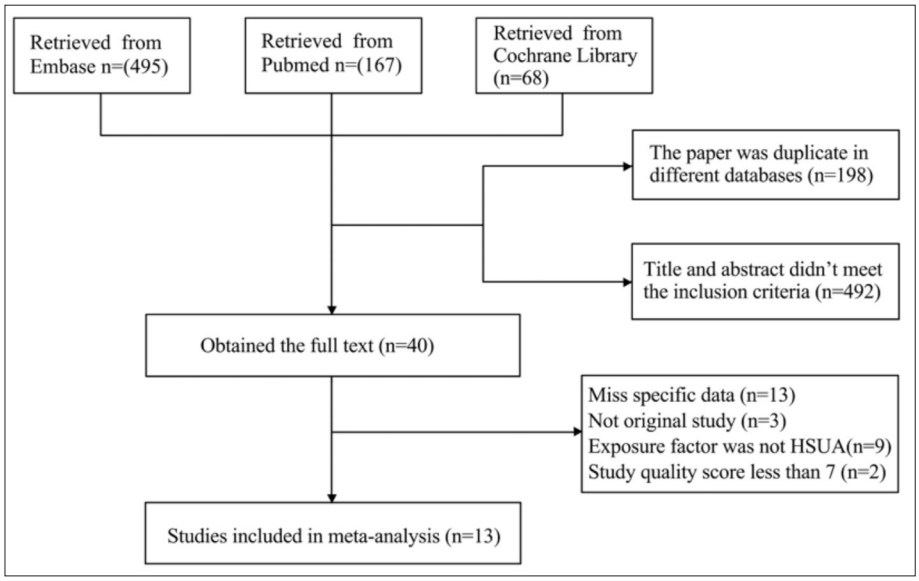

Figure 1 - Flow chart summarizing the procedure of studies selection for the meta-analysis. HSUA - high serum uric acid

Table 1 - Characteristics of included studies in the meta-analysis that investigated whether serum uric acid (SUA) level affects the prognosis of patients with AMI.

Study/year	Study type	Sample size	Age mean±SD		Follow-up (mean)	Cut-off of HSUA	PCI	Type of AMI	Variable controlled	Study quality
			Exposure	Control						
Gazi et al[18]2014	Retrospective	586	(66)	(60)	6.7 days	7mg/dL(M) 6mg/dL(W)	PCI	STEMI	Age	7
Akgul et al[19]2014	Prospective	434	56.8±13.9	54.8±11.6	6 months	5.7mg/dL(C)	PCI	STEMI	Age	8
Lazzeri et al[20]2012	Prospective	866	(73.4)	(76.0)	in hospital	6.2mg/dL(C)	PCI	STEMI	Age	7
Omidvar et al[21]2012	Retrospective	184	61.79±12.99	55.7±10.76	30 days	7.0mg/dL(M) 5.6mg/dL(W)	PCI/non-PCI	STEMI	Age, RF, hypothyroidism, gout, malignancy	8
Chen et al[22]2012	Retrospective	502	61.51±14.01	61.19±14.06	in hospital (12.06 days)	420umol/L(M) 357umol/L(W)	PCI/non-PCI	STEMI	Age, liver and kidney diseases, gout, alcoholism	7
Kaya et al[23]2012	Retrospective	2249	60.5±12.6	55.9±11.6	24.3 months	7mg/dL(M) 6mg/dL(W)	PCI	STEMI	Age,	8
Akpek et al[24]2011	Retrospective	289	60±12		in hospital	5.4mg/dL(C)	PCI	STEMI	Age,thrombolytic, gout, malignancy, liver and renal failure	9
Bae et al[25]2011	Retrospective	850	68.9±11.7	66.5±11.7	6 months	7.05mg/dL(C)	PCI/non-PCI	STEMI/ NSTEMI	Age, LVEF	9
Basar et al[26]2011	Retrospective	185	60.4±9.8	58.2±9.7	1 years	6.5mg/dL(C)	PCI	STEMI	Age	8
Lazzeri et al[27]2010	Prospective	466	72	64	<30 days	6.5mg/dL(C)	PCI	STEMI	Age	8
Kowalczyk et al[28] 2010	Prospective	1015	67±10.2	64.3±10.6	37.5 months	420umol/l(C)	PCI	STEMI	Age	8
Car S & Trkulja [29] 2009	Retrospective	621	27-90		13 years	7.00mg/dL(M) 6.05mg/dL(W)	PCI/non-PCI	STEMI/ NSTEMI	Age	8
Kojima et al[30]2005	Retrospective	1124	/	/	669 days	447umol/L(C)	PCI/non-PCI	STEMI/ NSTEMI	/	7

SD - standard deviation, HSUA - high serum uric acid, M - man, W - women, C - combined, PCI - percutaneous coronary intervention, AMI - acute myocardial infarction, STEMI - ST-elevation myocardial infarction, NSTEMI - non ST-elevation myocardial infarction, RF- renal function, LVEF - left ventricular ejection fraction

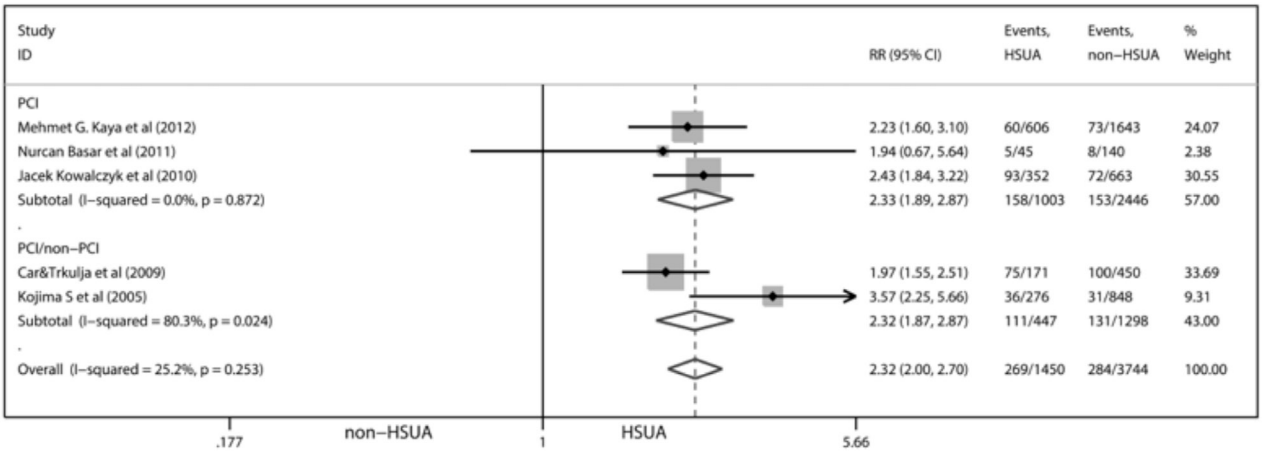

Figure 2 - Forest plot for random effects analysis of risks of AMI mid/long-term morbidity associated with HSUA. AMI - acute myocardial infarction, PCI - percutaneous coronary intervention, HSUA - high werum acid, RR - relative risk, CI - confidence interval

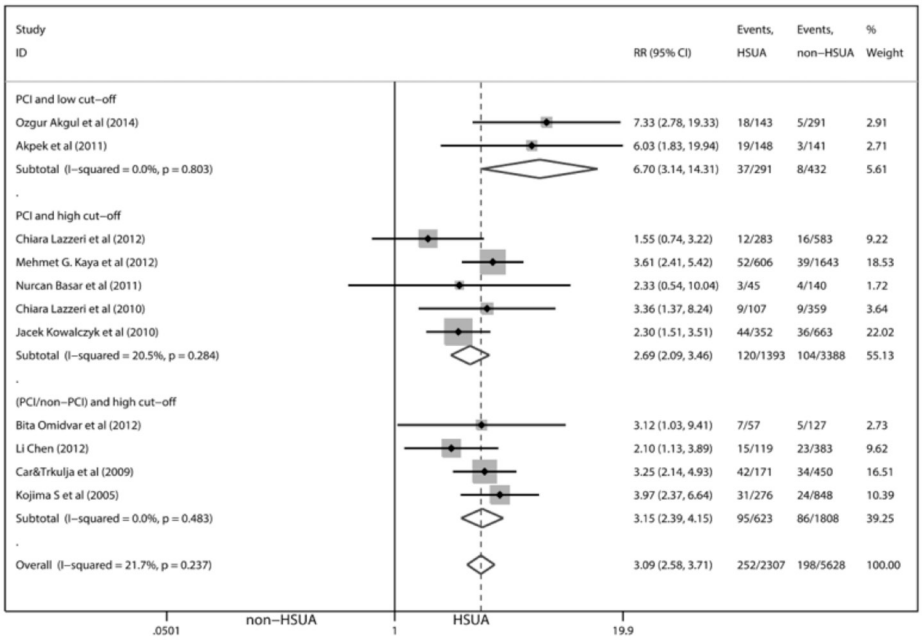

Figure 3 - Forest plot for random effects analysis of risks of AMI short-term morbidity associated with HSUA. AMI - acute myocardial infarction, PCI - percutaneous coronary intervention, HSUA - high werum acid, RR - relative risk, CI - confidence interval

heterogeneity of the studies.[13] The heterogeneity level was quantified by using the I^2.[14] Based on the severity of the heterogeneity, I^2<25%, 25≤I^2<50%, and I^2≥50% are generally considered as no heterogeneity, mild heterogeneity, and indicative of large heterogeneity, respectively.[14,15] The publication bias (significance level p<0.1) was assessed by using the Begg funnel plots.[16,17] We performed a subgroup analysis on whether all the patients in the study cohort were treated with PCI. All the data were analyzed by using Stata 12.0 (Stata Corp, College Station, TX, USA).

Results. *Literature search.* The electronic searches identified 730 records, wherein 13 studies[18-30] met the inclusion criteria. **Figure 1** describes the specific selection process of literature. If the same paper exists in multiple databases, we retained the paper of one database; thus, 198 papers were excluded. We excluded 492 papers because the title and abstract did not meet the inclusion criteria. We obtained the full text of 40 studies, wherein 13 were excluded because specific data were not included (for example, HSUA cut-off level, FUT, number of deaths). Three papers were not an

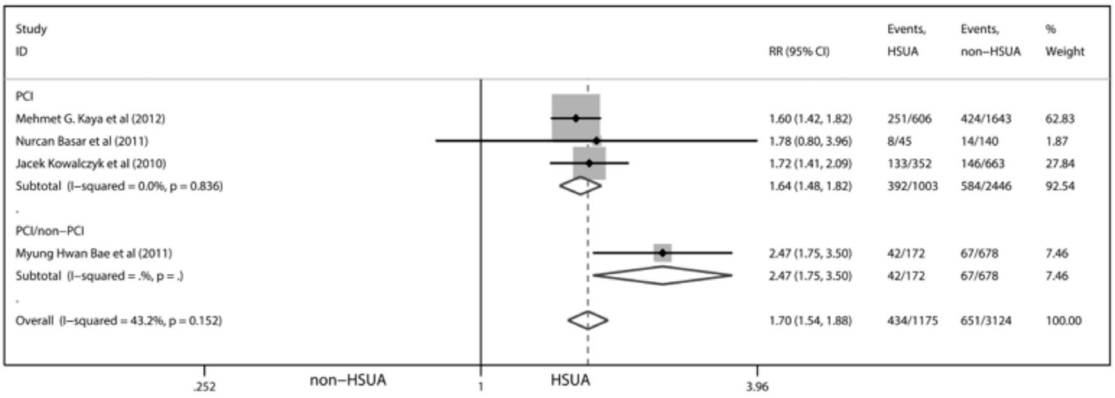

Figure 4 - Forest plot for random effects analysis of risks of AMI mid/long-term MACE risk associated with HSUA. AMI - acute myocardial infarction, PCI - percutaneous coronary intervention, HSUA - high werum acid, RR - relative risk, CI - confidence interval

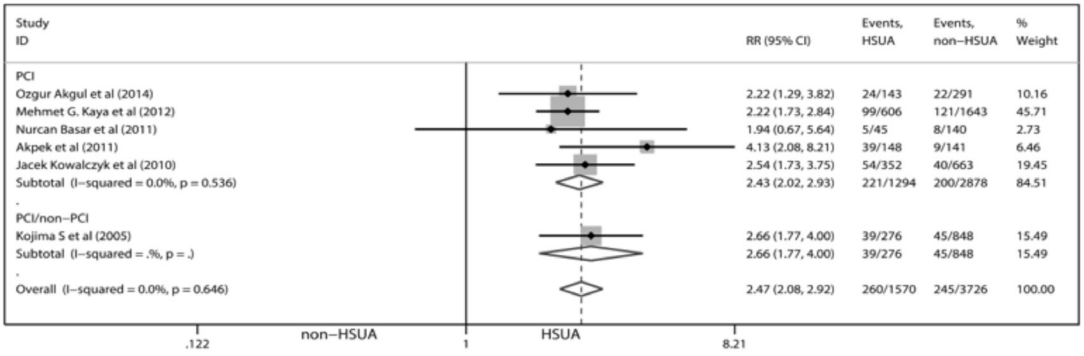

Figure 5 - Forest plot for random effects analysis of risks of AMI short-term MACE risk associated with HSUA. AMI - acute myocardial infarction, PCI - percutaneous coronary intervention, HSUA - high werum acid, RR - relative risk, CI - confidence interval

original study. Nine studies were excluded because the exposure factor was not SUA or hyperuricemia. Two studies were excluded because NOS score was <7.

Description of studies. This analysis included 13 studies with 9371 patients. The inclusion criteria of 8 studies[18-20,23,24,26-28] were patients who were diagnosed with acute ST-elevation myocardial infarction (STEMI) and underwent PCI subsequently. The inclusion criteria of 2 studies[21,22] were patients with STEMI, but did not control their treatment plan. Another three studies[25,29,30] did not control whether these patients underwent PCI and included patients with STEMI and non-STEMI (NSTEMI) in the cohort. The FUT of seven studies,[19,23,25,26,28-30] was >6 months and <30 days for the others.[18,20-22,24,27] All these studies had clear HSUA cut-off level. Two studies'[19,24] particularly had a cut-off lower (5.4 mg/dL and 5.7 mg/dL) than other studies. Six studies[19,23,26,28-30] reported mid/long-term mortality, and 5 studies[19,23,25,26,28] reported mid/long-term MACE. Twelve studies[18-24,26-30] reported short-term mortality, and 6 studies[19,23,24,26,28,30] reported short-term MACE. The characteristics of these studies are shown in **Table 1**.

Mid/long-term (≥6 months) mortality. Six studies (5628 participants) reported mid/long-term mortality, wherein 2 studies[29,30] included patients with STEMI and NSTEMI in the cohort, and did not control whether these patients underwent PCI; 4 studies[19,23,26,28] included only patients with STEMI who underwent PCI. HSUA was associated with higher mid/long-term mortality (RR=2.43, 95% CI: 2.10–2.82). A study heterogeneity was observed (I^2=50.4%, p=0.073). After excluding the study[19] with significantly lower HSUA cut-off level than other studies, the effect was not much changed (RR=2.32, 95% CI: 2.00–2.70). Nonetheless, the heterogeneity was found to be significantly decreased (I^2=25.2%, p=0.253) (**Figure 2**), and no publication bias was observed by the Begg test (z=0.24, p=0.806). In the subgroup analysis on whether patients underwent PCI, the effect (RR=2.33, 95% CI: 1.89–2.87) had almost no difference in the group that mixed patients who underwent PCI and those who did not (RR=2.32, 95% CI: 1.87–2.87), and no heterogeneity (I^2=0.0%, p=0.872) was found among these studies that only included patients who underwent PCI (**Figure 2**).

Therefore, the heterogeneity among studies may be due to the fact that some studies have not controlled whether patients underwent PCI or not, as well as differences in the critical value of HSUA in various studies.

Short-term (≤30 days) mortality. Twelve studies (8521 participants) reported short-term mortality, wherein 2 studies[29,30] included patients with STEMI and NSTEMI in the cohort and did not control whether these patients underwent PCI; eight studies[18-20,23-28] included only patients with STEMI who underwent PCI. Two studies[21,22] included only patients with STEMI, but did not control whether these patients underwent PCI. The HSUA was associated with higher short-term mortality (RR=3.19, 95% CI: 2.68–3.79). Mild heterogeneity (I^2=26.0%, p=0.189) and no publication bias by the Begg test (z=0.07, p=0.945) were observed. After excluding the study18 with the shortest FUT, the effect was not much changed (RR=3.09, 95% CI: 2.58–3.71). However, among-study heterogeneity (I^2=21.7%, p=0.237) (**Figure 3**) was significantly decreased, and no publication bias by the Begg test (z=0.00, p=1.00) was found. In the subgroup analysis on whether the patients underwent PCI and HSUA cut-off level, the HSUA was associated with higher short-term mortality (RR=2.69, 95% CI: 2.09–3.46) (**Figure 3**) in the PCI and high cut-off subgroups, higher short-term mortality (RR=6.70, 95% CI: 3.14–14.31) (**Figure 3**) in the PCI and low cut-off subgroups. The heterogeneity among studies was likely attributable to the short FUT.

Mid/long-term (≥6 months) MACE. Five studies (4733 participants) reported mid/long-term MACE, wherein one study[25] included patients with STEMI and NSTEMI in the cohort and did not control whether these patients underwent PCI; 4 studies[19,23,26,28] included only patients with STEMI who underwent PCI. HSUA was associated with higher mid/long-term MACE (RR=1.74, 95% CI: 1.58–1.92) with mild heterogeneity (I^2=48.9%, p=0.098) and no publication bias by the Begg test (z=0.73, p=0.462). After excluding the study[19] with significantly lower HSUA cut-off level than that in other studies, the effect was not much changed (RR=1.70, 95% CI: 1.54–1.88). The study heterogeneity (I^2=43.2%, p=0.152) (**Figure 4**) decreased, and no publication bias by the Begg test (z=0.34, p=0.734) was observed. In a subgroup analysis of studies that included only patients who underwent PCI, the mid/long-term MACE RR was not much changed (RR=1.64, 95% CI: 1.48–1.82), but the among-study heterogeneity (I^2=0%, p=0.836) decreased significantly (**Figure 4**). The heterogeneity among studies was mainly attributable to the AMI type and whether patients underwent PCI.

Short-term (≤30 days) MACE. Six studies (5296 participants) reported short-term MACE, wherein one study[30] included patients with STEMI and NSTEMI in the cohort and did not control whether these patients underwent PCI; 5 studies[19,23,24,26,28] included only patients with STEMI who underwent PCI. HSUA was associated with higher short-term MACE (RR=2.47, 95% CI: 2.08–2.92), no heterogeneity (I^2=0.00%, p=0.646) (**Figure 5**), and no publication bias by the Begg test (z=0.38, p=0.707). In the PCI subgroup, the short-term MACE risk (RR=2.43, 95% CI: 2.02–2.93) was not different with the PCI/non-PCI subgroup (**Figure 5**).

Discussion. The main finding of this systematic review and meta-analysis showed that HSUA level (including hyperuricemia and high-normal values) significantly increased short-term mortality (<30 days), mid/long-term mortality (>6 months), short-term MACE, and mid/long-term MACE of patients after AMI. Furthermore, a clear subgroup analysis was performed by different HSUA cut-off levels, different treatments (whether these patients underwent PCI), different AMI types, etc. The association is still statistically significant. With respect to short-term mortality, the HSUA cut-off level in two studies was significantly lower than that in other studies, and the RR of overall effect of the two studies were significantly higher than that of other study patients. This might indicate that the mild increase in SUA level (normal range) begun to significantly affect the short-term prognosis of patients who underwent PCI after STEMI, and this conclusion has not been raised before.

Uric acid is a xanthine metabolite and plays a role as an antioxidant. During tissue ischemia, xanthine oxidoreductase might catalyze xanthine to uric acid, and uric acid appeared as compensatory increase.[31-36] Recent studies have established that uric acid was associated with cardiovascular disease. Patients with AMI with high SUA levels were found to more likely die than those with lower SUA levels.[37,38] Therefore, high uric acid levels might be a risk factor for MACE and mortality even in younger patients (<35 years) with AMI.[39-41] Angiotensin receptor blocker and statins were well known to be useful for patients with metabolic syndrome. Metabolic syndrome was identified as a multiple risk factor (high blood pressure, visceral obesity, dyslipidemia, and dysglycemia) for cardiovascular disease.[42-44] Some reviews suggested that hyperuricemia (with or without urate deposition) can be considered as a component of the metabolic syndrome.[44,45] Recent studies confirm that uric acid weakened the role

of losartan, atorvastatin, and fenofibrate to reduce cardiovascular risk.[46-48] Furthermore, allopurinol can reduce the casual and 24-h ambulatory blood pressure of adolescent patients with newly diagnosed hypertension compared with placebo in a random trial.[49,50] A study including 245 consecutive patients with stable angina pectoris showed that a significant increase in SUA level may cause platelet resistance for patients with CHD.[51] However, some studies showed that the SUA level did not influence the response of platelet to ticagrelor, clopidogrel, and aspirin,[52] and SUA level did not increase platelet aggregation during dual antiplatelet therapy whether aspirin was combined with tigriolor or combined with clopidogrel.[53] Nevertheless, it needed a large random clinical trial and long-term follow up to determine the safety and efficacy of lowering UA therapy in cardiovascular disease.

This meta-analysis has several limitations. First, most studies were retrospective. Although these studies considered a multitude of lifestyle, diet, and comorbidities, many unmeasured and residual confounding factors in studies difficult to rule out must be acknowledged. Second, the design of each study cannot be perfectly consistent. Some differences were found among these studies with respect to age range, FUT, AMI type, and so on. Hence, the inherent limitation to this meta-analysis is the potential heterogeneity among these studies. Third, the differences in various factors in PCI surgery might increase heterogeneity among studies of the PCI subgroup. Finally, the HSUA cut-off level was different in each study, with some as high as 7.5 mg/dL and some as low as 5.4 mg/dL, but the HSUA cut-off level in most of these studies (10/13) was between 6 mg/dL and 7 mg/dL. We have done our best to evaluate the comprehensive effect by removing the study with significantly lower or higher HSUA cut-off levels than those in other studies.

This study also has some strengths. The sample size of these studies included in this meta-analysis was relatively large. Assessment of the quality of each study for a systematic review is necessary. However, there was no unified view regarding which method is the best to evaluate the quality of studies. We chose the NOS[12] to evaluate these studies, and the NOS includes three important elements on evaluating cohort studies. The quality of the studies included in this meta-analysis was higher. We performed subgroup analysis on whether patients underwent PCI after AMI and calculated the RRs for mortality and MACE of patients who underwent PCI after AMI (STEMI).We found that the short-term mortality was significantly increased by the mildly elevated SUA levels in patients who underwent PCI after AMI, and the short-term mortality was worse than the group with higher HSUA cut-off levels.

In conclusion, this meta-analysis evidenced that HSUA level increased the mortality and risk of MACE whether short-term or mid/long-term and whether PCI was performed after AMI. Particularly, the mild elevation of SUA levels (normal range) might have begun to have a significant increase in the short-term mortality of patients with STEMI and those who underwent PCI. However, this should be conferred with further investigations and research, and this reminded us that the relative value of elevated uric acid level after PCI may be more worthy of our attention than the absolute value of uric acid.

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