Abstract: Objective: The current study aimed to explore the predictive ability of serum uric acid (SUA) in patients suffering from acute ST segment elevation myocardial infarction (STEMI). Method: PubMed, EMBASE, Cochrane Library, and Medline databases were systematically searched from their respective inceptions to February 2018. Systematic analysis and random-effects meta-analysis of prognostic effects were performed to evaluate STEMI outcomes [i.e., in-hospital mortality, one-year mortality, in-hospital Major Adverse Cardiovascular Events (MACE)] in relation to SUA. Results: A total of 12 studies (containing 7,735 patients with acute STEMI) were identified (5,562 low SUA patients and 3,173 high SUA patients). Systematic analysis of these studies showed that high SUA patients exhibited a higher incidence of in-hospital MACE (OR, 2.30; P < 0.00001), in-hospital mortality (OR, 3.03; P < 0.0001), and one-year mortality (OR, 2.58; P < 0.00001), compared with low SUA patients. Conclusions: Acute STEMI patients with high SUA exhibited an elevated incidence rate of in-hospital MACE, in-hospital mortality, and one-year mortality. Further randomized controlled trials will be needed to verify these results.

Keywords: serum uric acid (SUA), ST segment elevation myocardial infarction (STEMI), mortality, Major Adverse Cardiovascular Events (MACE), meta-analysis

1 Introduction

The effects of serum uric acid (SUA) on the in-hospital and one-year follow-up prognosis in patients with acute ST segment elevation myocardial infarction (STEMI) are debatable, and clinical application of its measurement remains uncertain. Uric acid (UA) is the end-point degradation product of purine nucleotides and can be synthesized by several different types of tissue, including those outside the muscles of the cardiovascular system. Within tissues, UA increases rapidly and is then released into the vascular lumen. Once there, a decrease in intracellular pH and a reversal of negative membrane potential occurs. According to studies, synthesis of UA and the activity of xanthine oxidase both increase in cases of myocardial ischemia [1–3]. The Thrombolysis in Myocardial Infarction (TIMI) scores can be converted to clinical risk scores to develop prognoses for patients suffering from acute coronary syndrome. An increase or decrease in UA/xanthine oxidase status is used to determine risk factor [4]. A previous study from our lab discovered that the level of SUA is closely related to patients with acute STEMI [5, 6]. Thus, SUA can be used as a predictor of STEMI in patients. Furthermore, studies have shown that the inclusion of SUA in risk scores increases the accuracy risk prediction. The current study conducted a meta-analysis to explore the difference between high and low SUA in STEMI patients.

2 Methods

2.1 Search methods

PubMed, EMBASE, Ovid Medline, and Cochrane Library databases were systematically searched from their respective inceptions through to February 2018. The following MeSH terms and keywords were included in the search strategy to identify articles in English: “uric acid
Egger’s tests were conducted to evaluate publication bias and small research effects.

3 Results

3.1 Study selection

A total of 1,421 articles were identified involving both UA and acute STEMI from the PubMed, Medline, EMBASE, and Cochrane databases (through February 2018). Of these, 524 repeated articles were excluded, and 852 articles were found to be inappropriate given the goals of the current study. The full texts of 45 studies were carefully reviewed. A total of 12 studies, with a total of 7,357 patients, were analyzed (Figure 1) [7–18]. Table 1 shows baseline characteristics of the analyzed studies and Table 2 presents the population characteristics for each study.

3.2 Begg’s funnel plot analysis and quality assessment

A Begg’s funnel plot showed no obvious asymmetry in the prognostic value of SUA in acute STEMI. Furthermore, all of the studies were evaluated as demonstrating a low risk of bias. Therefore, it is concluded that the meta-analysis exhibits no obvious publication bias. The quality assessment of RCTs included in this meta-analysis is shown in Figure 2.

3.3 Outcome of In-hospital MACE

The incidence of in-hospital MACE during the in-hospital period was 13.5% in high SUA patients vs. 6.6% in low SUA patients. According to the five studies which provided data for in-hospital MACE, no heterogeneity was observed amongst the results (P = 0.41, I² =0%). The incidence of in-hospital MACE in the high SUA group was significantly higher than that in the low SUA group (OR, 2.30; 95% CI, 1.83–2.88; P < 0.00001; Figure 3).

3.4 Outcomes of In-hospital mortality

The incidence of in-hospital mortality during the in-hospital period was 9.2% in high SUA patients vs. 3.4% in low SUA patients, which was a statistically significant difference (I² = 0%; OR: 3.03, 95% CI: 1.78–5.13; P < 0.0001; Figure 4).
1421 records identified through PubMed, Embase, Medline and Cochrane Library electronic databases.

524 repeated articles were removed

897 of articles assessed for eligibility

852 articles irrelevant with our study were removed.

45 of full-text articles appear to meet

33 studies removed for reviews (n=3) or meta-analyses (1) letters (n=4) or no relevant clinical results (n=25).

12 of studies included in meta-analysis

Figure 1. Search strategy conducted for all included trials. Abbreviations: MeSH, medical subject headings.

Table 1. Baseline characteristics of randomized studies.

| Randomized studies | Year | Sample size | Low UA | High UA | Inclusion criteria | Exclusion criteria | Endpoints | Follow-up period |
|--------------------|------|-------------|--------|---------|--------------------|--------------------|------------|-----------------|
| Basar et al 2011    | 140  | 45          |        |         | All patients with the diagnosis of STEMI within 12 hours from the onset of symptoms, cardiogenic shock within 24 hours. | Patients with culprit lesion in the left main coronary artery, previous CABG, end-stage renal disease, hepatic or hemolytic disorders, concomitant inflammatory diseases, neoplastic diseases, recent major surgical procedures, trauma, and any systemic disorders. | All-cause mortality, Major Adverse Cardiovascular Events. | During hospitalization or one year |
| Wang et al 2012     | 178  | 98          |        |         | Patients with the diagnosis of STEMI within 12 hours from the onset of symptoms undergoing primary PCI. | Patients with thrombolysis treatment within 24 hours, concomitant inflammatory diseases, autoimmune disorders, neoplastic diseases, liver or kidney failure. | Major Adverse Cardiovascular Events. | During hospitalization |
| Mehmet et al 2012   | 1643 | 606         |        |         | STEMI patients with underwent primary PCI. | PCI was not performed, UA values were missing or unavailable, or no follow-up was documented after primary PCI. | All-cause mortality, Major Adverse Cardiovascular Events. | During hospitalization |
| Li et al 2012       | 383  | 119         |        |         | Consecutive patients with STEMI, given standard treatment. | The patients who had liver and kidney diseases, gout, alcoholism and violent exercise. | All-cause mortality. | During hospitalization |
| Randomized studies | Year | Sample size | Inclusion criteria | Exclusion criteria | Endpoints | Follow-up period |
|--------------------|------|-------------|--------------------|-------------------|-----------|-----------------|
| Bita et al 2012    | 2012 | 127 57      | The patients with acute STEMI. | Not receive thrombolytic therapy during the first six hours after the onset of chest pain; cardiogenic shock; previous pacemaker implantation; a recent myocardial infarction (<3 months); severe valvular disease; renal function impaired (serum creatinine level >1.5 mg/dl); cases of hypothyroidism, malignancy, gout or other inflammatory diseases and using corticosteroid or cytotoxic drugs. | All-cause mortality. | During hospitalization |
| Chiara et al 2012  | 2012 | 436 207     | Consecutive patients with STEMI (within 12 h from symptoms onset) after primary percutaneous coronary intervention (PCI). | no exclusion criteria. | All-cause mortality. | During hospitalization |
| Ozgur et al 2014   | 2014 | 291 143     | Patients with STEMI, > 30 minutes of continuous typical chest pain, ST-segment elevation / 2 mm in two contiguous electrocardiography leads within 12 hours of symptom onset, or evidence of continuing ischemia or hemodynamic instability for up to 18 hours. | Patients with no indication of PCI, not suitable for PCI, missing or unavailable data about uric acid level upon admission. | All-cause mortality, Major Adverse Cardiovascular Events. | During hospitalization |
| Emine et al 2014   | 2014 | 479 107     | Patients with STEMI. | patients who had no UA measurements and who had to be sent to another cardiology center for rescue percutaneous transluminal coronary angioplasty (PTCA). | All-cause mortality. | During hospitalization |
| Chiara et al 2015  | 2015 | 220 109     | Patients with STEMI (within 12 h from symptoms onset), submitted to primary PCI, and eGFR below 60 ml/min/1.73m². | no exclusion criteria. | All-cause mortality | During hospitalization or one year |
| Reza et al 2016    | 2016 | 518 90      | Patients with STEMI. | Patients with liver disease, progressive kidney disorders (creatinine >1.8), gout, alcoholism or taking antihyperuricemic drugs. Patients with previous history of diuretic and losartan use, also patients with previous history of MI. | All-cause mortality | During hospitalization |
The prediction of cardiac events in patients with acute ST segment elevation myocardial infarction

| Randomized studies | Year | Sample size | Inclusion criteria                                                                 | Exclusion criteria                                                                                                                                                                                                 | Endpoints                                      | Follow-up period                     |
|---------------------|------|-------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------|
| Mora-Ramirez et al  | 2017 | 504         | Patients with STEMI, SUA measurement on admission; underwent myocardial reperfusion therapy (thrombolytic therapy or primary percutaneous coronary intervention) within 12 hours of onset. | Patients with current use of uric acid-lowering drugs (e.g. allopurinol, probenecid, benz bromarone) or thiazides, active neoplastic disease, end-stage renal disease with dialysis, history of gouty arthritis or urolithiasis; and missing values in the data registry. | All-cause mortality, Major Adverse Cardiovascular Events. | During hospitalization                |
| Cheng-Wei et al     | 2017 | 643         | The STEMI patients who presented to our Emergency Department directly.              | Patients without definite door-to-balloon time, mainly those who were transferred from another hospital, those who were transferred from our outpatient department, and those who had in-hospital STEMI.                  | All-cause mortality.                           | one year                             |

Table 2. Patient characteristics in each randomized trial.

| Study      | Groups (SUA) | Age mean | Male sex (n) | Smoking history (n) | Hypertension (n) | Diabetes mellitus (n) | Previous aspirin(n) |
|------------|--------------|----------|--------------|--------------------|------------------|----------------------|---------------------|
| Basar et al| Low          | 58.2 ±9.7| 112          | 85                 | 40               | 29                   | 33                  |
|           | High         | 60.4 ± 9.8| 36           | 30                 | 21               | 10                   | 12                  |
| Wang et al | Low          | 56 ±11    | 139          | 106                | 89               | 45                   | 17                  |
|           | High         | 57±11     | 82           | 66                 | 50               | 26                   | 10                  |
| Mehmet et al| Low        | 55.9±11.6 | 1393         | 960                | 585              | 370                  | NA                  |
|           | High         | 60.5±12.6 | 460          | 306                | 308              | 172                  | NA                  |
| Li et al   | Low          | 61.19±14.06| 335         | NA                 | 197              | 110                  | NA                  |
|           | High         | 61.51±14.01| 82         | NA                 | 60               | 41                   | NA                  |
| Bita et al | Low          | NA        | 99           | 69                 | 40               | 42                   | NA                  |
|           | High         | NA        | 28           | 16                 | 28               | 21                   | NA                  |
| Chiara et al| Low         | NA        | NA           | NA                 | NA               | NA                   | NA                  |
|           | High         | NA        | 28           | 16                 | 28               | 21                   | NA                  |
| Ozgur et al | Low         | 54.8±11.6 | 70           | 223                | 97               | 61                   | NA                  |
|           | High         | 56.8±13.9 | 23           | 98                 | 54               | 28                   | NA                  |
| Emine et al| Low          | 60        | 81           | 176                | 142              | 185                  | 496                 |
|           | High         | 66        | 38           | 34                 | 28               | 45                   | 102                 |
| Chiara et al| Low         | NA        | 111          | 76                 | 160              | 70                   | NA                  |
|           | High         | NA        | 66           | 55                 | 72               | 25                   | NA                  |
| Reza et al | Low          | 61.8±13.4 | 378          | NA                 | 216              | 96                   | NA                  |
|           | High         | 67.5±12.4 | 58           | NA                 | 51               | 21                   | NA                  |
| Mora-Ramirez et al| Low   | 57.6±11.3 | 448          | 304                | 206              | 195                  | 501                 |
|           | High         | 61.2±11.9 | 220          | 156                | 158              | 115                  | 288                 |
| Cheng-Wei et al| Low       | 56        | 571          | 428                | 366              | 165                  | 635                 |
|           | High         | 58        | 263          | 188                | 183              | 70                   | 290                 |

NA: not available
Figure 2. Assessment of the quality of selected RCTs. Low risk of bias (green circles), unclear risk of bias (yellow circles) and high risk of bias (red circles).

| Study or Subgroup       | High UA | Low UA | Odds Ratio | Odds Ratio |
|-------------------------|---------|--------|------------|------------|
|                         | Events  | Total  | Weight     | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Basar et al 2011        | 5       | 45     | 8          | 140        | 3.7% | 2.06 [0.64, 6.66] |
| Mehmet et al 2012       | 99      | 606    | 121        | 1643       | 63.4% | 2.46 [1.85, 3.26] |
| Mora-Ramirez et al 2017 | 26      | 291    | 29         | 504        | 16.9% | 1.61 [0.93, 2.79] |
| Ozgur et al 2014        | 24      | 143    | 22         | 291        | 13.4% | 2.47 [1.33, 4.57] |
| Wang et al 2012         | 6       | 98     | 3          | 178        | 2.6%  | 3.80 [0.93, 15.56] |
| Total (95% CI)          | 1183    | 2756   | 100.0%     | 2.30 [1.83, 2.88] |
| Total events            | 160     | 183    |             |             |

Heterogeneity: $Tau^2 = 0.00; \ Chisq = 2.41, df = 4 (P = 0.66); I^2 = 0$

Figure 3. Fixed-effect meta-analysis for In-hospital MACE. The figure presents the number of events, the number of patients in the treatment and control groups, the odds ratio (OR) and 95% confidence interval (CI) for each trial, the overall OR estimate with 95% CI and the P value for the association test, the P value for the heterogeneity test, and between-trial inconsistency ($I^2$) measures.
The prediction of cardiac events in patients with acute ST segment elevation myocardial infarction

Oxidoreductase inhibitor, which reduces levels of SUA, exerts protective effects in the context of oxidative stress (e.g., ischemia-reperfusion injury and cardiovascular disease) [20-22]. UA can be detected before other cardiac markers, such as cardiac troponins. Thus, SUA is suitable to be an early marker of myocardial ischemia, making it an effective method for predicting the combination of myocardial infarction and troponins.

Previous studies have examined the prognostic features of suitable biomarkers for atherosclerotic cardiovascular disease [23-25]. Although SUA appears to assist in the clinical evaluation of patients, the level of impact of SUA can have in medical treatment or in improving prognosis remains unclear [26]. According to the current meta-analysis, mortality and MACE were elevated in the high SUA group during the in-hospital period than that observed in the low SUA group. Regardless of the low heterogeneity found, the MACE and mortality of high SUA patients with acute STEMI were significantly different. The data indicated that the number of acute STEMI patients suffering from MACE in the high SUA group during the in-hospital period was approximately 2 times larger than individuals with oxidoreductase inhibitor, which reduces levels of SUA, exerts protective effects in the context of oxidative stress (e.g., ischemia-reperfusion injury and cardiovascular disease) [20-22]. UA can be detected before other cardiac markers, such as cardiac troponins. Thus, SUA is suitable to be an early marker of myocardial ischemia, making it an effective method for predicting the combination of myocardial infarction and troponins.

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3.5 Outcome of one-year mortality

The incidence of one-year mortality during the follow-up period was 14.4% in high SUA patients vs. 6.1% in low SUA patients, which represented a significant difference (P = 0%; OR: 2.5, 95%CI: 1.75–3.80; P < 0.00001; Figure 5).

4 Discussion

There was no significant difference between Egger’s test results and those patients studied. Based on the funnel plot analysis, a consistency was observed between the symmetry and publication bias. UA is the final degradation product of purine metabolism. The value of SUA was shown in our meta-analysis as an effective prognostic biomarker of future adverse events in acute STEMI patients. To the best of our knowledge, previous analyses have not elucidated the potential clinical value of SUA in this way [19].

Evidence from current epidemiological studies have shown that elevated SUA levels are an important risk factor for cardiovascular disease, with oxidative stress playing an important pathophysiological role. In addition, xanthine oxidoreductase inhibitor, which reduces levels of SUA, exerts protective effects in the context of oxidative stress (e.g., ischemia-reperfusion injury and cardiovascular disease) [20-22]. UA can be detected before other cardiac markers, such as cardiac troponins. Thus, SUA is suitable to be an early marker of myocardial ischemia, making it an effective method for predicting the combination of myocardial infarction and troponins.

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low SUA. In addition, the mortality rate of patients with high SUA during hospitalization was approximately 2.7 times larger in high SUA, when compared to low SUA individuals. Moreover, the incidences of one-year mortality presented a statistically significant difference between high and low SUA patients, with high SUA patients being approximately 2.36 times more likely to die within one year than low SUA patients. It was also found that an increase in SUA level was associated to an increase in risk of coronary ischemia. However, there is not enough evidence to suggest myocyte necrosis. Therefore, the current results suggest that a high level of SUA will lead to an increase in MACE, in-hospital mortality, and one-year mortality in acute STEMI patients.

There are two caveats with the current study which should be considered carefully. Firstly, due to the lack of professional RCTs focusing on this research, we only extracted data from observational studies, which can certainly lead to a risk of related bias. Secondly, all 12 articles involved in this meta-analysis came from different study groups within different countries. Thus the diagnostic criteria for SUA cutoff may also have differed.

5 Conclusions

Acute STEMI patients suffering from high SUA exhibit higher incidences of in-hospital MACE and in-hospital mortality. Further, the mortality rate was also significantly higher in this group within one year. While SUA might facilitate the advancement of atherosclerosis, it might also serve as a new prognostic marker for short- and long-term follow-up in patients with acute STEMI [21]. Additionally, this measure may become pivotal in clinical prognosis, possibly improving the accuracy of current risk stratification methods. This may be able to assist in the development of more effective medical treatment, the reduction in health care cost, and an improvement in the quality of life of patients by reducing re-hospitalization and medical expenses. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Conflict of interest: Authors state no conflict of interest.

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