Serum uric acid on admission cannot predict long-term outcome of critically ill patients: a retrospective cohort study

Qinchang Chen¹,*, Kai Huang²,*, Lingling Li², Xixia Lin², Cong Ding², Junrui Zhang³, Qingui Chen¹

¹Department of Medical Intensive Care Unit, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; ²Division of Vascular and Thyroid surgery, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; ³Guangzhou Institute of Standardization, Guangzhou, China

*These authors contributed equally to this work

Purpose: We aimed to evaluate the association of serum uric acid on admission with long-term outcome of critically ill patients.

Materials and methods: We conducted a retrospective cohort study using data extracted from the Medical Information Mart for Intensive Care III database. The primary endpoint was 90-day mortality. Propensity score matching (PSM) was performed, and multivariate Cox regression analysis was used to adjust for potential confounders. Receiver operating characteristic (ROC) curves were also used to assess the mortality predictions.

Results: A total of 2,123 patients were included finally with a PSM cohort consisting of 556 90-day non-survivors matched 1:1 with 556 90-day survivors. No statistically significant difference of median admission uric acid was observed between the two groups (survivors 5.50 mg/dL vs non-survivors 5.60 mg/dL, \( p = 0.536 \)). ROC area under the curve was 0.511 (95% confidence interval [CI] 0.477–0.545), suggesting that uric acid had poor discriminative powers for predicting 90-day mortality. No significant association between uric acid and 90-day mortality was found (hazard ratio 1.00, 95% CI 0.98–1.03, \( p = 0.6835 \)).

Conclusion: Serum uric acid on intensive care unit admission failed to predict 90-day mortality of critically ill patients.

Keywords: uric acid, critical care, mortality, risk factors

Introduction

Uric acid, the end product of an exogenous pool of purines, which functions as either an antioxidant or a pro-oxidant, has been reported as a predictor of outcomes in multiple diseases.¹⁻⁴ Related research studies focused mainly on cardiovascular disease and found that uric acid might serve as a biomarker of severity of coronary artery disease in patients with acute coronary syndrome, cardiovascular mortality, 1-year mortality of patients with acute coronary syndromes treated with percutaneous coronary intervention, and might improve the prognostic accuracy of some clinical models.⁵⁻⁸ The prognostic and predictive value of uric acid was also explored in type 2 diabetic patients and patients who had open heart surgery.⁹,¹⁰ However, the value of initial serum uric acid on admission in critically ill patients seems limited. Akbar et al reported that elevated uric acid levels in patients with sepsis are associated with an increased risk of acute kidney injury and acute respiratory distress syndrome, but Zhu et al found that there was no correlation between the initial levels of serum uric acid and prognosis of infection in critically ill patients.¹¹,¹² Meanwhile, it has been reported that no relationship was found between serum uric acid and...
short-term mortality of critically ill patients.\textsuperscript{13,14} To the best of our knowledge, there is no research to evaluate the association of serum uric acid on intensive care unit (ICU) admission with long-term outcome of critically ill patients. Thus, we performed a retrospective cohort study using a modifiable data mining technique applied to the publicly available Medical Information Mart for Intensive Care III (MIMIC-III) database, aiming to clarify whether there is an association between admission serum uric acid levels and long-term outcome.\textsuperscript{15}

Materials and methods
Study design and data sources
We conducted a retrospective cohort study using data extracted from the MIMIC-III database, which is a large publicly available database consisting of de-identified health-related data of patients who had stayed in the ICU of Beth Israel Deaconess Medical Center between 2001 and 2012. Access to database has been approved by the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates. No informed consent was required on the de-identified patients.

Participants
Adult patients (aged $\geq$18 years) of first hospital admission and first ICU admission were considered and included, but patients staying at ICU for <1 day and patients without admission serum uric acid records were excluded. In addition, patients whose death was earlier than ICU admission time and patients whose length of hospital stay was less than length of ICU stays were excluded in order to exclude potential typographical errors and records of organ donor account (Figure 1).

Variables
We applied Structured Query Language to extract data from the database mainly by using codes from the MIMIC Code Repository.\textsuperscript{16,24} Age, sex, ICU mortality and hospital mortality, length of ICU stay and length of hospital stay, 28-day mortality and 90-day mortality, admission serum uric acid (admission was defined as within 24 hours after ICU admission), Simplified Acute Physiology Score II (SAPS II), the Elixhauser comorbidities, and the Elixhauser Comorbidity Index (SID30) were extracted or calculated.\textsuperscript{17–19} Missing components for the calculation of SAPS II were treated as normal (usually 0). Because the database has had date of birth of patients who are older than 89 years shifted to exactly 300 years before to obscure their age, we corrected them (age $-$300+89) before analysis.

Outcome measures
Ninety-day mortality after ICU admission was chosen as the primary end point, and 28-day mortality, hospital mortality, and ICU mortality were secondary outcomes. ICU mortality was determined only by the first ICU stay.

Propensity score matching (PSM)
We grouped the study subjects as survivors and non-survivors according to their 90-day survival status after ICU admission. The propensity score for each patient was calculated to estimate their probability of death during the first 90 days after ICU admission by using multivariable logistic regression models given the following covariates: gender, age, SAPS II, Elixhauser Comorbidity Index (SID30), sepsis (based on International Classification of Diseases, Ninth Revision [ICD-9] codes), mechanical ventilation on the first day, renal replacement therapy on the first day, congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorder, peripheral vascular disorder, hypertension, paralysis, other neurological disease, chronic pulmonary disease, uncomplicated diabetes, complicated
diabetes, hypothyroidism, renal failure, liver disease, peptic ulcer, acquired immune deficiency syndrome, lymphoma, metastatic cancer, solid tumor, rheumatoid arthritis, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychoses, and depression. Matching was performed with the use of a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width equal to 0.05 of the standard deviation of the log of the propensity score. The overlap of the distribution of the propensity scores across survivors and non-survivors groups is shown in Figure S1.

Statistical analysis
For continuous variables, data were expressed as median and interquartile range (IQR) unless otherwise stated. For categorical variables, data were shown as numbers and percentages. Comparison of continuous and categorical variables was performed using Kruskal-Wallis and chi-square (or Fisher’s exact) tests, respectively. We used receiver operating characteristic (ROC) curves to evaluate the prognostic predictive value of serum uric acid for 90-day mortality and other outcomes and used the Kaplan–Meier (K-M) method and log-rank tests to compare survival differences among patients of different admission serum uric acid levels. Variables associated with 90-day mortality were evaluated by univariate Cox regression analysis, and those with a p-value <0.1 were considered in multivariable Cox regression model. Considering the expected collinearity between comorbidities and the Elixhauser Comorbidity Index (SID30), we would choose only either one of them to be enrolled into one adjusted model when variables are potentially significant (p<0.1) in univariate analysis. Age was not included in the multivariable regression analysis since it was factored into SAPS II. Multivariable Cox regression model was performed to evaluate the association of serum uric acid on 90-day mortality and 28-day mortality, and multivariable logistic regression model was used to examine the association between hospital mortality and ICU mortality. p-values of <0.05 were considered to indicate statistical significance. Empower(R) (www.empowerstats.com; X&Y solutions, Inc., Boston, MA, USA) and R software, version 3.4.3 (http://www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

Results
Patient characteristics
A total of 2,123 patients were included (Figure 1). As shown in Table 1, the median age of the study patients was 64.09 years (IQR 51.39–75.74 years) and 1,219 of the 2,123 cases (57.42%) were male. The median admission serum uric acid was 5.40 mg/dL (IQR 3.80–7.90 mg/dL) with a median SAPS II score of 39 (IQR 30–49). Among them, 239 (11.26%) patients were diagnosed with sepsis based on ICD-9 codes and 1,032 (48.61%) patients required mechanical ventilation on admission. The five most common comorbidities were fluid and electrolyte disorders (38.48%), congestive heart failure (20.35%), deficiency anemia (20.16%), cardiac arrhythmias (20.07%), and coagulopathy (19.31%). The 90-day mortality was 27.23% with 578 non-survivors and 1,545 survivors. The length of ICU stay and hospital stay was 3.79 (IQR 2.01–9.19) and 14.69 (IQR 8.05–26.37) days, respectively. Non-survivors had significantly higher SAPS II (p<0.001). No statistically significant difference was observed in serum uric acid between survivors and non-survivors.

Characteristics of the PSM cohort
A total of 556 non-survivors were successfully matched with one control. Characteristics of PSM cohort are shown in Table 2. There was no statistically significant difference between survivors and non-survivors in age, gender, SAPS II on admission, Elixhauser Comorbidity Index (SID30), and comorbidities (p>0.05), and no statistically significant difference was found on serum uric acid between survivors and non-survivors.

Survival status of patients with different serum uric acid levels on admission
Patients were grouped according to their serum uric acid levels on admission. The K-M survival curves presented in Figure 2 showed that there was no difference in the survival rate among different serum uric acid levels on admission (log-rank test: p=0.88) after PSM. The K-M survival curves of 28-day mortality are shown in Figure S2.

ROC curve analysis
As shown in Figure 3, the area under the ROC curve (AUC) of admission serum uric acid for discrimination of 90-day survivors and non-survivors was 0.522 (95% confidence interval [CI] 0.494–0.550) and 0.511 (95% CI 0.477–0.545) for all patients and PSM cohort, respectively. ROC curve analysis of other outcomes also indicated a poor predictive value of serum uric acid.

Association between serum uric acid levels on admission and ICU outcomes
Results of univariate Cox regression analysis of all patients and PSM cohort are presented in Tables S1 and S2, respectively. Results of univariate Cox regression analysis of all patients and PSM cohort are presented in Tables S1 and S2, respectively. Parameters of different admission serum uric acid levels on admission and ICU outcomes

As shown in Figure S2, the ROC analysis of other outcomes also indicated a poor predictive value of serum uric acid.
Table 1  Characteristics and comparison between survivors and non-survivors of all patients

| Variable                        | All patients (n=2,123) | Survivors (n=1,545) | Non-survivors (n=578) | p-value |
|---------------------------------|------------------------|---------------------|-----------------------|---------|
| Age (years)                     | 64.09 (51.39–75.74)    | 62.11 (48.68–73.83) | 68.97 (57.79–79.52)   | <0.001  |
| Male                            | 1,219 (57.42%)         | 895 (57.93%)        | 324 (56.06%)          | 0.437   |
| ICU mortality                   | 187 (8.81%)            | 0 (0.00%)           | 187 (32.35%)          | <0.001  |
| Hospital mortality              | 379 (17.85%)           | 4 (0.26%)           | 375 (64.88%)          | <0.001  |
| Length of ICU stay (days)       | 3.79 (2.01–9.19)       | 3.47 (1.94–9.14)    | 4.21 (2.31–9.31)      | 0.001   |
| Length of hospital stay (days)  | 14.69 (8.05–26.37)     | 14.32 (7.90–26.00)  | 15.84 (9.03–27.50)    | 0.051   |
| Uric acid on admission (mg/dL)  | 5.40 (3.80–7.90)       | 5.30 (3.80–7.80)    | 5.70 (3.90–8.00)      | 0.119   |
| SAPS II on admission            | 39 (30–49)             | 36.00 (28.00–45.00) | 47.00 (39.00–56.00)   | <0.001  |
| Elixhauser Comorbidity Index (SID30) | 11.00 (4.00–23.00)     | 11.00 (0.00–20.00)  | 17.00 (11.00–28.00)   | <0.001  |
| Sepsis (based on ICD-9 codes)   | 239 (11.26%)           | 132 (8.54%)         | 107 (18.51%)          | <0.001  |
| Mechanical ventilation on first day | 1,032 (48.61%)        | 754 (48.80%)        | 287 (48.10%)          | 0.772   |
| Renal replacement therapy on first day | 135 (6.36%)          | 93 (6.02%)          | 42 (7.27%)            | 0.295   |

Comorbidities

| Variable                        | Survivors (n=1,545) | Non-survivors (n=578) | p-value |
|---------------------------------|---------------------|-----------------------|---------|
| Congestive heart failure        | 432 (20.35%)        | 268 (17.35%)          | 164 (28.37%) | <0.001 |
| Cardiac arrhythmias             | 426 (20.07%)        | 268 (17.35%)          | 158 (27.34%) | <0.001 |
| Valvular disease                | 109 (5.13%)         | 67 (4.34%)            | 42 (7.27%)  | 0.006  |
| Pulmonary circulation disorder  | 110 (5.18%)         | 70 (4.53%)            | 40 (6.92%)  | 0.027  |
| Peripheral vascular disorder    | 185 (8.71%)         | 130 (8.41%)           | 55 (9.52%)  | 0.423  |
| Hypertension                    | 239 (11.26%)        | 169 (10.94%)          | 70 (12.11%) | 0.447  |
| Paralysis                       | 51 (2.40%)          | 36 (2.33%)            | 15 (2.60%)  | 0.723  |
| Other neurological disease      | 182 (8.57%)         | 127 (8.22%)           | 55 (9.52%)  | 0.343  |
| Chronic pulmonary disease       | 327 (15.40%)        | 238 (15.40%)          | 89 (15.40%) | 0.997  |
| Uncomplicated diabetes          | 365 (17.19%)        | 267 (17.28%)          | 98 (16.96%) | 0.859  |
| Complicated diabetes            | 133 (6.26%)         | 96 (6.21%)            | 37 (6.40%)  | 0.874  |
| Hypothyroidism                  | 170 (8.01%)         | 126 (8.16%)           | 44 (7.61%)  | 0.682  |
| Renal failure                   | 302 (14.23%)        | 212 (13.72%)          | 90 (15.57%) | 0.278  |
| Liver disease                   | 152 (7.16%)         | 98 (6.34%)            | 54 (9.34%)  | 0.017  |
| Peptic ulcer                    | 1 (0.05%)           | 1 (0.06%)             | 0 (0.00%)   | 1.000  |
| AIDS                            | 15 (0.71%)          | 10 (0.63%)            | 5 (0.87%)   | 0.569  |
| Lymphoma                       | 89 (4.19%)          | 55 (3.56%)            | 34 (5.88%)  | 0.017  |
| Metastatic cancer               | 121 (5.70%)         | 54 (3.50%)            | 67 (11.59%) | <0.001 |
| Solid tumor                     | 59 (2.78%)          | 43 (2.78%)            | 16 (2.77%)  | 0.985  |
| Rheumatoid arthritis            | 49 (2.31%)          | 31 (2.01%)            | 18 (3.11%)  | 0.130  |
| Coagulopathy                    | 410 (19.31%)        | 252 (16.31%)          | 158 (27.34%) | <0.001 |
| Obesity                         | 84 (3.96%)          | 61 (3.95%)            | 23 (3.98%)  | 0.974  |
| Weight loss                     | 127 (5.98%)         | 80 (5.18%)            | 47 (8.13%)  | 0.011  |
| Fluid and electrolyte disorders | 817 (38.48%)        | 548 (35.47%)          | 269 (46.54%) | <0.001 |
| Blood loss anemia               | 72 (3.39%)          | 65 (4.21%)            | 7 (1.21%)   | <0.001 |
| Deficiency anemia               | 428 (20.16%)        | 322 (20.84%)          | 106 (18.34%) | 0.201  |
| Alcohol abuse                   | 116 (5.46%)         | 91 (5.89%)            | 25 (4.33%)  | 0.158  |
| Drug abuse                      | 56 (2.64%)          | 49 (3.17%)            | 7 (1.21%)   | 0.012  |
| Psychoses                       | 68 (3.20%)          | 59 (3.82%)            | 9 (1.56%)   | 0.008  |
| Depression                      | 112 (5.28%)         | 86 (5.57%)            | 26 (4.50%)  | 0.327  |

Notes: Patients were grouped as survivors and non-survivors determined by 90-day mortality status. Data are expressed as median (interquartile range) or n (%) unless otherwise stated. Kruskal–Wallis and chi-square (or Fisher's exact) tests were used to analyse continuous and categorical variables, respectively. Statistical significance (p<0.05) is shown in bold.

Abbreviations: ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; ICD-9, International Classification of Diseases, Ninth Revision; AIDS, acquired immune deficiency syndrome.

respectively. As shown in Table 3, multivariable regression analysis of PSM cohort indicated that serum uric acid was not an independent risk factor of 90-day mortality (hazard ratio [HR] 1.00, 95% CI 0.98–1.03, p=0.6835), 28-day mortality (HR 1.01, 95% CI 0.98–1.04, p=0.4894), hospital mortality (odds ratio [OR] 1.01, 95% CI 0.97–1.04, p=0.6099), and ICU mortality (OR 1.01, 95% CI 0.97–1.05, p=0.6934).

Results of regression analysis of all patients are also shown in Table 3.

Discussion

For the first time, the present study evaluated the association between serum uric acid on ICU admission and long-term outcome of critically ill patients. Results of the study
indicated that serum uric acid on admission cannot predict long-term outcome of critically ill patients.

It is interesting to find no correlation between serum uric acid with clinical outcomes of critically ill patients, since many studies had reported the prognostic predictive value of serum uric acid in many clinical conditions. For example, uric acid was found to be an independent predictor of cardiovascular outcomes and increase prognostic accuracy of Cox models in hypertensives with normal renal function which allowed a risk reclassification according to a recent report of Perticone et al.

Given serum uric acid is increased in respiratory disease, especially in the presence of hypoxia and systemic inflammation, many researchers wondered whether it could serve as a biomarker of prognostic predictive value. Nagaya et al reported that serum uric acid levels correlate with the severity and the mortality of primary pulmonary

**Table 2 Characteristics and comparison between survivors and non-survivors of PSM cohort**

| Variable                               | All patients (n=1,112) | Survivors (n=556) | Non-survivors (n=556) | p-value |
|----------------------------------------|------------------------|-------------------|-----------------------|---------|
| Age (years)                            | 69.00 (57.80–79.00)    | 69.13 (58.27–78.71) | 68.97 (57.44–79.54)   | 0.920   |
| Male                                   | 621 (55.85%)           | 306 (55.04%)      | 315 (56.65%)          | 0.587   |
| ICU mortality                          | 176 (15.83%)           | 0 (0.00%)         | 176 (31.65%)          | <0.001  |
| Hospital mortality                     | 358 (32.19%)           | 3 (0.54%)         | 355 (63.85%)          | <0.001  |
| Length of ICU stay (days)              | 4.08 (2.16–9.48)       | 3.81 (2.08–9.42)  | 4.29 (2.39–9.49)      | 0.164   |
| Length of hospital stay (days)         | 15.98 (8.82–28.13)     | 16.18 (8.64–29.04) | 15.87 (9.09–27.52)    | 0.687   |
| Uric acid on admission (mg/dL)         | 5.50 (3.80–8.20)       | 5.50 (3.70–8.30)  | 5.60 (3.90–7.90)      | 0.536   |
| SAPS II on admission                   | 46.00 (37.00–55.00)    | 45.00 (37.00–55.00) | 46.00 (38.00–55.00)   | 0.202   |
| Elixhauser Comorbidity Index (SiD30)   | 18.00 (10.00–28.00)    | 19.00 (9.75–28.00) | 17.00 (10.75–27.25)   | 0.428   |
| Mechanical ventilation on first day    | 184 (16.55%)           | 83 (14.93%)       | 101 (18.17%)          | 0.146   |
| Renal replacement therapy on first day | 531 (47.75%)           | 263 (47.30%)      | 268 (48.20%)          | 0.764   |

**Comorbidities**

| Variable                          | Survivors (n=556) | Non-survivors (n=556) | p-value |
|-----------------------------------|-------------------|-----------------------|---------|
| Congestive heart failure          | 167 (30.04%)      | 154 (27.70%)          | 0.390   |
| Cardiac arrhythmias               | 148 (26.62%)      | 149 (26.80%)          | 0.946   |
| Valvular disease                  | 38 (6.83%)        | 42 (7.55%)            | 0.642   |
| Pulmonary circulation disorder    | 41 (7.37%)        | 39 (7.01%)            | 0.816   |
| Peripheral vascular disorder      | 52 (9.35%)        | 53 (9.53%)            | 0.918   |
| Hypertension                      | 71 (12.77%)       | 68 (12.23%)           | 0.786   |
| Paralysis                         | 16 (2.88%)        | 14 (2.52%)            | 0.711   |
| Other neurological disease        | 53 (9.35%)        | 53 (9.53%)            | 1.000   |
| Chronic pulmonary disease         | 95 (17.09%)       | 88 (15.83%)           | 0.571   |
| Uncomplicated diabetes            | 97 (17.45%)       | 97 (17.45%)           | 1.000   |
| Complicated diabetes              | 39 (7.01%)        | 33 (5.94%)            | 0.465   |
| Hypothyroidism                    | 51 (9.17%)        | 41 (7.37%)            | 0.276   |
| Renal failure                     | 95 (17.09%)       | 87 (15.65%)           | 0.517   |
| Liver disease                     | 48 (8.63%)        | 49 (8.81%)            | 0.915   |
| AIDS                              | 7 (1.26%)         | 5 (0.90%)             | 0.773   |
| Lymphoma                          | 34 (6.12%)        | 34 (6.12%)            | 1.000   |
| Metastatic cancer                 | 44 (7.91%)        | 55 (9.89%)            | 0.247   |
| Solid tumor                       | 19 (3.42%)        | 16 (2.88%)            | 0.606   |
| Rheumatoid arthritis              | 18 (3.24%)        | 17 (3.06%)            | 0.864   |
| Coagulopathy                      | 146 (26.26%)      | 146 (26.26%)          | 1.000   |
| Obesity                           | 20 (3.60%)        | 22 (3.96%)            | 0.753   |
| Weight loss                       | 47 (8.45%)        | 46 (8.27%)            | 0.914   |
| Fluid and electrolyte disorders   | 258 (46.40%)      | 251 (45.14%)          | 0.674   |
| Blood loss anemia                 | 4 (0.72%)         | 7 (1.26%)             | 0.547   |
| Deficiency anemia                 | 114 (20.50%)      | 104 (18.71%)          | 0.450   |
| Alcohol abuse                     | 25 (4.50%)        | 23 (4.14%)            | 0.768   |
| Drug abuse                        | 5 (0.90%)         | 7 (1.26%)             | 0.773   |
| Psychoses                         | 12 (2.16%)        | 9 (1.62%)             | 0.509   |
| Depression                        | 26 (4.68%)        | 25 (4.50%)            | 0.886   |

**Notes:** Patients were grouped as survivors and non-survivors determined by 90-day mortality status. Data are expressed as median (interquartile range) or n (%) unless otherwise stated. Kruskal–Wallis and chi-square (or Fisher’s exact) tests were used to analyze continuous and categorical variables, respectively. Statistical significance (p<0.05) is shown in bold.

**Abbreviations:** PSM, propensity score matching; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; ICD-9, International Classification of Diseases, Ninth Revision; AIDS, acquired immune deficiency syndrome.
hypothesis. Bartziokas et al found that serum uric acid was associated with increased 30-day mortality and risk for future acute exacerbation of chronic obstructive pulmonary disease. Ergun et al reported that high serum uric acid levels are predictive for not only long-term mortality but also for short-term mortality. However, in terms of critically ill patients, only a few studies were conducted to explore the value of uric acid and most of the conclusions were negative. Considering that most of the previous studies evaluated only the short-term outcomes with limited sample sizes, we conducted this present study aiming to evaluate the predictive value of serum uric acid for long-term outcome of critically ill patients. In our study, we included over 2,000 patients which made enough adjustment for confounders available and improved statistical power. Meanwhile, we performed PSM to further minimize the potential selection bias. Results of all patients and PSM cohort were consistent and provided a solid conclusion of the association between

Figure 2 Kaplan–Meier survival curve by different levels of uric acid of all patients and PSM cohort.
Abbreviations: ICU, intensive care unit; PSM, propensity score matching.

Figure 3 (Continued)
Serum uric acid cannot predict long-term outcome of critically ill patients, although negative. We also examined some short-term outcomes in the study, and the results were consistent with previous studies.

Although the findings in our study were informative, there were several limitations in the present study. First, given the observational nature of our study, it is not possible to adjust all potential confounders. Although we considered...
Table 3  Association of uric acid with 90-day mortality, 28-day mortality, ICU mortality, and hospital mortality

| Subjects           | HR/OR   | 95% CI     | p-value  |
|--------------------|---------|------------|----------|
| All patients       |         |            |          |
| 90-day mortality   |         |            |          |
| Non-adjusted       | 1.02    | 1.00–1.05  | 0.0552   |
| Model I            | 1.00    | 0.98–1.03  | 0.7743   |
| Model II           | 1.01    | 0.98–1.03  | 0.5735   |
| 28-day mortality   |         |            |          |
| Non-adjusted       | 1.03    | 1.00–1.06  | 0.0571   |
| Model I            | 1.01    | 0.98–1.04  | 0.6281   |
| Model II           | 1.01    | 0.98–1.04  | 0.5785   |
| ICU mortality      |         |            |          |
| Non-adjusted       | 1.03    | 0.99–1.08  | 0.1198   |
| Model I            | 1.01    | 0.96–1.05  | 0.8157   |
| Model II           | 1.00    | 0.96–1.05  | 0.9105   |
| Hospital mortality |         |            |          |
| Non-adjusted       | 1.04    | 1.00–1.07  | 0.0301   |
| Model I            | 1.01    | 0.97–1.04  | 0.6263   |
| Model II           | 1.01    | 0.97–1.04  | 0.6924   |
| PSM cohort         |         |            |          |
| 90-day mortality   |         |            |          |
| Non-adjusted       | 1.01    | 0.98–1.03  | 0.6160   |
| Model I            | 1.00    | 0.98–1.03  | 0.6835   |
| 28-day mortality   |         |            |          |
| Non-adjusted       | 1.01    | 0.98–1.04  | 0.3784   |
| Model I            | 1.01    | 0.98–1.04  | 0.4894   |
| ICU mortality      |         |            |          |
| Non-adjusted       | 1.02    | 0.98–1.07  | 0.3709   |
| Model I            | 1.01    | 0.97–1.05  | 0.6934   |
| Hospital mortality |         |            |          |
| Non-adjusted       | 1.02    | 0.98–1.05  | 0.3751   |
| Model I            | 1.01    | 0.97–1.04  | 0.6099   |

Notes: Association of uric acid with 90-day mortality and 28-day mortality was analyzed using Cox regression models, and associations of uric acid with ICU mortality and hospital mortality were analyzed using logistic regression models. For all patients, model I was adjusted for SAPS II, Elixhauser Comorbidity Index (SID30), and sepsis based on ICD-9 codes; model II was adjusted for SAPS II, sepsis based on ICD-9 codes, congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorder, liver disease, lymphoma, metastatic cancer, coagulopathy, weight loss, fluid and electrolyte disorders, blood loss anemia, drug abuse, and psychoses. For PSM cohort, model was adjusted for SAPS II. Statistical significance (p<0.05) is shown in bold.

Abbreviations: ICU, intensive care unit; HR, hazard ratio; OR, odds ratio; CI, confidence interval; PSM, propensity score matching; SAPS II, Simplified Acute Physiology Score II; ICD-9, International Classification of Diseases, Ninth Revision.

Conclusion

This large retrospective cohort study found that there was no statistically significant association of admission serum uric acid with 90-day mortality of ICU patients, providing a stronger confirmation of the controversial issue. However, further prospective basic and clinical research studies are still needed especially to reveal the underlined mechanisms and to evaluate the potential predictive value of changes of uric acid.

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Author contributions

Qingui Chen designed the study and was the primary author of the manuscript. Qinchang Chen and Kai Huang mainly performed data extraction and statistical analysis. All authors contributed toward data analysis, drafting, and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.
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Supplementary materials

Figure S1 Distribution of propensity scores.

Figure S2 Kaplan–Meier survival curve of 28-day mortality.
Abbreviations: ICU, intensive care unit; PSM, propensity score matching.
### Table S1 Univariate Cox regression analysis of all patients on 90-day mortality

| Variables                                | HR   | 95% CI        | p-value  |
|------------------------------------------|------|---------------|----------|
| Age (years)                              | 1.02 | 1.02–1.03     | <0.0001  |
| Gender                                   |      |               |          |
| Male                                     | 1.0  |               |          |
| Female                                   | 1.07 | 0.91–1.26     | 0.4272   |
| SAPS II                                  | 1.04 | 1.03–1.04     | <0.0001  |
| Sepsis (based on ICD-9 codes)            |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 2.02 | 1.63–2.49     | <0.0001  |
| Mechanical ventilation on first day      |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.99 | 0.84–1.16     | 0.8727   |
| Renal replacement therapy on first day   |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.22 | 0.89–1.67     | 0.2207   |
| Uric acid (mg/dl)                        | 1.02 | 1.00–1.05     | 0.0552   |
| Elixhauser Comorbidity Index (SID30)     | 1.04 | 1.03–1.04     | <0.0001  |
| Comorbidities                            |      |               |          |
| Congestive heart failure                 |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.67 | 1.40–2.01     | <0.0001  |
| Cardiac arrhythmias                      |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.60 | 1.33–1.92     | <0.0001  |
| Valvular disease                         |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.53 | 1.12–2.10     | 0.0078   |
| Pulmonary circulation disorder           |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.41 | 1.02–1.95     | 0.0357   |
| Peripheral vascular disorder             |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.10 | 0.83–1.45     | 0.5042   |
| Hypertension                             |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.08 | 0.84–1.38     | 0.5602   |
| Paralysis                                |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.08 | 0.65–1.81     | 0.7581   |
| Other neurological disease               |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.12 | 0.85–1.48     | 0.4238   |
| Chronic pulmonary disease                |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.01 | 0.81–1.27     | 0.9319   |
| Uncomplicated diabetes                   |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.97 | 0.78–1.20     | 0.7806   |
| Complicated diabetes                     |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.01 | 0.73–1.41     | 0.9442   |
| Hypothyroidism                           |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.93 | 0.68–1.27     | 0.6455   |
| Renal failure                            |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.11 | 0.89–1.39     | 0.3518   |

(Continued)

### Table S1 (Continued)

| Variables                                | HR   | 95% CI        | p-value  |
|------------------------------------------|------|---------------|----------|
| Liver disease                            |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.38 | 1.04–1.82     | 0.0246   |
| Peptic ulcer                             |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.00 | 0.00–Inf      | 0.9866   |
| AIDS                                     |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.19 | 0.49–2.88     | 0.6938   |
| Lymphoma                                 |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.47 | 1.04–2.08     | 0.0294   |
| Metastatic cancer                        |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 2.63 | 2.04–3.39     | <0.0001  |
| Solid tumor                              |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.99 | 0.61–1.64     | 0.9836   |
| Rheumatoid arthritis                     |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.44 | 0.90–2.30     | 0.1302   |
| Coagulopathy                             |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.71 | 1.43–2.06     | <0.0001  |
| Obesity                                  |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.04 | 0.68–1.57     | 0.8648   |
| Weight loss                              |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.42 | 1.06–1.92     | 0.0205   |
| Fluid and electrolyte disorders          |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 1.47 | 1.25–1.73     | <0.0001  |
| Blood loss anemia                        |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.31 | 0.15–0.65     | 0.0021   |
| Deficiency anemia                        |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.87 | 0.70–1.07     | 0.1879   |
| Alcohol abuse                            |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.76 | 0.51–1.13     | 0.1709   |
| Drug abuse                               |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.41 | 0.20–0.87     | 0.0198   |
| Psychoses                                |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.45 | 0.24–0.88     | 0.0188   |
| Depression                               |      |               |          |
| No                                       | 1.0  |               |          |
| Yes                                      | 0.81 | 0.55–1.20     | 0.2953   |

**Note:** Statistical significance (p<0.05) is shown in bold.

**Abbreviations:** HR, hazard ratio; CI, confidence interval; SAPS II, Simplified Acute Physiology Score II; ICD-9, International Classification of Diseases-Ninth Revision; AIDS, acquired immune deficiency syndrome; SID, State Inpatient Database.
### Table S2 Univariate Cox regression analysis of PsM cohort on 90-day mortality

| Variable                              | HR     | 95% CI     | p-value |
|---------------------------------------|--------|------------|---------|
| Age (years)                           | 1.00   | 0.99–1.00  | 0.5566  |
| Gender                                |        |            |         |
| Male                                  | 1.0    |            |         |
| Female                                | 0.95   | 0.80–1.13  | 0.5646  |
| SAPS II                               | 1.01   | 1.00–1.01  | 0.0606  |
| Sepsis (based on ICD-9 codes)         |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 1.16   | 0.93–1.43  | 0.1866  |
| Mechanical ventilation on first day   |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 1.04   | 0.88–1.23  | 0.6044  |
| Renal replacement therapy on first day|        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.98   | 0.71–1.34  | 0.8889  |
| Uric acid (mg/dL)                     | 1.01   | 0.98–1.03  | 0.6160  |
| Elixhauser Comorbidity Index (SID30)  | 1.00   | 0.99–1.00  | 0.3701  |
| Comorbidities                         |        |            |         |
| Congestive heart failure              |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.91   | 0.76–1.10  | 0.3262  |
| Cardiac arrhythmias                   |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.99   | 0.82–1.19  | 0.9074  |
| Valvular disease                      |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 1.05   | 0.77–1.44  | 0.7671  |
| Pulmonary circulation disorder        |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.94   | 0.68–1.30  | 0.7088  |
| Peripheral vascular disorder          |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.97   | 0.73–1.29  | 0.8432  |
| Hypertension                          |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.93   | 0.72–1.19  | 0.5546  |
| Paralysis                             |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.88   | 0.52–1.50  | 0.6503  |
| Other neurological disease            |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.96   | 0.72–1.27  | 0.7778  |
| Chronic pulmonary disease             |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.97   | 0.77–1.21  | 0.7744  |
| Uncomplicated diabetes                |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.98   | 0.79–1.22  | 0.8543  |
| Complicated diabetes                  |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.85   | 0.60–1.21  | 0.3748  |
| Hypothyroidism                        |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.83   | 0.60–1.13  | 0.2361  |
| Renal failure                         |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.90   | 0.71–1.13  | 0.3562  |

### Table S2 (Continued)

| Variable                              | HR     | 95% CI     | p-value |
|---------------------------------------|--------|------------|---------|
| Liver disease                         | 1.0    |            |         |
| No                                    |        |            |         |
| Yes                                   | 0.98   | 0.73–1.32  | 0.9022  |
| AIDS                                  |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.72   | 0.30–1.73  | 0.4603  |
| Lymphoma                              |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.94   | 0.67–1.33  | 0.7409  |
| Metastatic cancer                     |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 1.14   | 0.86–1.50  | 0.3634  |
| Solid tumor                           |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.89   | 0.54–1.46  | 0.6411  |
| Rheumatoid arthritis                  |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.94   | 0.58–1.53  | 0.8061  |
| Coagulopathy                          |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.99   | 0.82–1.20  | 0.9481  |
| Obesity                               |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 1.17   | 0.76–1.79  | 0.4717  |
| Weight loss                           |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.93   | 0.69–1.26  | 0.6577  |
| Fluid and electrolyte disorders       |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.96   | 0.81–1.13  | 0.6048  |
| Blood loss anemia                     |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 1.27   | 0.60–2.67  | 0.5344  |
| Deficiency anemia                     |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.92   | 0.74–1.14  | 0.4309  |
| Alcohol abuse                         |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.94   | 0.62–1.43  | 0.7775  |
| Drug abuse                            |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 1.21   | 0.57–2.55  | 0.6186  |
| Psychoses                             |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.93   | 0.48–1.79  | 0.8215  |
| Depression                            |        |            |         |
| No                                    | 1.0    |            |         |
| Yes                                   | 0.94   | 0.63–1.41  | 0.7814  |

**Abbreviations:** PsM, propensity score matching; HR, hazard ratio; CI, confidence interval; SAPS II, Simplified Acute Physiology Score II; ICD-9, International Classification of Diseases-Ninth Revision; AIDS, acquired immune deficiency syndrome; SID, State Inpatient Database.
Serum uric acid cannot predict long-term outcome of critically ill patients