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ORIGINAL RESEARCH

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

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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

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short-term mortality of critically ill patients.[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.[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.

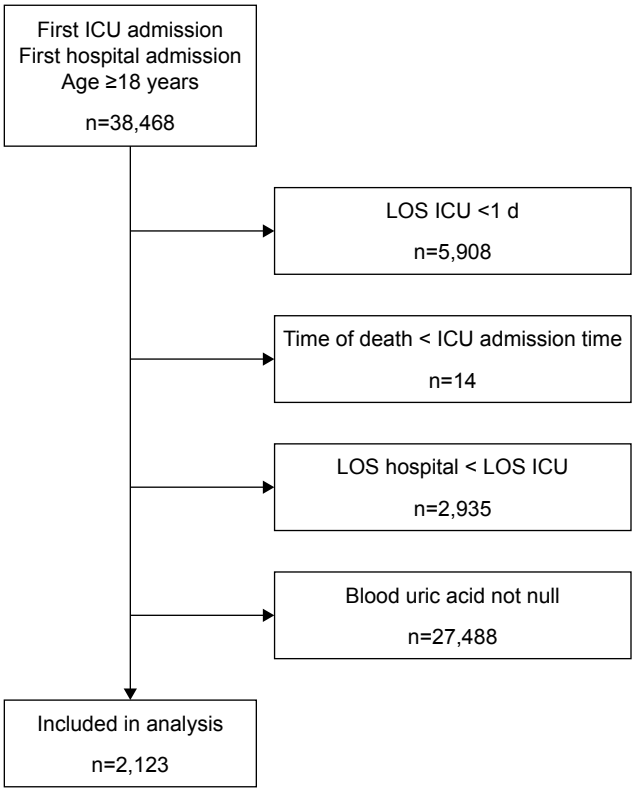

Figure 1 Flow chart of the study.
Abbreviations: ICU, intensive care unit; LOS, length of stay.

Participants

Adult patients (aged ≥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.[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 (State Inpatient Database [SID]30) were extracted or calculated.[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 logit 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,

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%)	278 (48.10%)	0.772
Renal replacement therapy on first day	135 (6.36%)	93 (6.02%)	42 (7.27%)	0.295
Comorbidities				
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 (0.65%)	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

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
Sepsis (based on ICD-9 codes)	184 (16.55%)	83 (14.93%)	101 (18.17%)	0.146
Mechanical ventilation on first day	531 (47.75%)	263 (47.30%)	268 (48.20%)	0.764
Renal replacement therapy on first day	86 (7.73%)	45 (8.09%)	41 (7.37%)	0.653
Comorbidities				
Congestive heart failure	321 (28.87%)	167 (30.04%)	154 (27.70%)	0.390
Cardiac arrhythmias	297 (26.71%)	148 (26.62%)	149 (26.80%)	0.946
Valvular disease	80 (7.19%)	38 (6.83%)	42 (7.55%)	0.642
Pulmonary circulation disorder	80 (7.19%)	41 (7.37%)	39 (7.01%)	0.816
Peripheral vascular disorder	105 (9.44%)	52 (9.35%)	53 (9.53%)	0.918
Hypertension	139 (12.50%)	71 (12.77%)	68 (12.23%)	0.786
Paralysis	30 (2.70%)	16 (2.88%)	14 (2.52%)	0.711
Other neurological disease	106 (9.53%)	53 (9.53%)	53 (9.53%)	1.000
Chronic pulmonary disease	183 (16.46%)	95 (17.09%)	88 (15.83%)	0.571
Uncomplicated diabetes	194 (17.45%)	97 (17.45%)	97 (17.45%)	1.000
Complicated diabetes	72 (6.47%)	39 (7.01%)	33 (5.94%)	0.465
Hypothyroidism	92 (8.27%)	51 (9.17%)	41 (7.37%)	0.276
Renal failure	182 (16.37%)	95 (17.09%)	87 (15.65%)	0.517
Liver disease	97 (8.72%)	48 (8.63%)	49 (8.81%)	0.915
AIDS	12 (1.08%)	7 (1.26%)	5 (0.90%)	0.773
Lymphoma	68 (6.12%)	34 (6.12%)	34 (6.12%)	1.000
Metastatic cancer	99 (8.90%)	44 (7.91%)	55 (9.89%)	0.247
Solid tumor	35 (3.15%)	19 (3.42%)	16 (2.88%)	0.606
Rheumatoid arthritis	35 (3.15%)	18 (3.24%)	17 (3.06%)	0.864
Coagulopathy	292 (26.26%)	146 (26.26%)	146 (26.26%)	1.000
Obesity	42 (3.78%)	20 (3.60%)	22 (3.96%)	0.753
Weight loss	93 (8.36%)	47 (8.45%)	46 (8.27%)	0.914
Fluid and electrolyte disorders	509 (45.77%)	258 (46.40%)	251 (45.14%)	0.674
Blood loss anemia	11 (0.99%)	4 (0.72%)	7 (1.26%)	0.547
Deficiency anemia	218 (19.60%)	114 (20.50%)	104 (18.71%)	0.450
Alcohol abuse	48 (4.32%)	25 (4.50%)	23 (4.14%)	0.768
Drug abuse	12 (1.08%)	5 (0.90%)	7 (1.26%)	0.773
Psychoses	21 (1.89%)	12 (2.16%)	9 (1.62%)	0.509
Depression	51 (4.59%)	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.

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.[8] 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.[20] Nagaya et al reported that serum uric acid levels correlate with the severity and the mortality of primary pulmonary

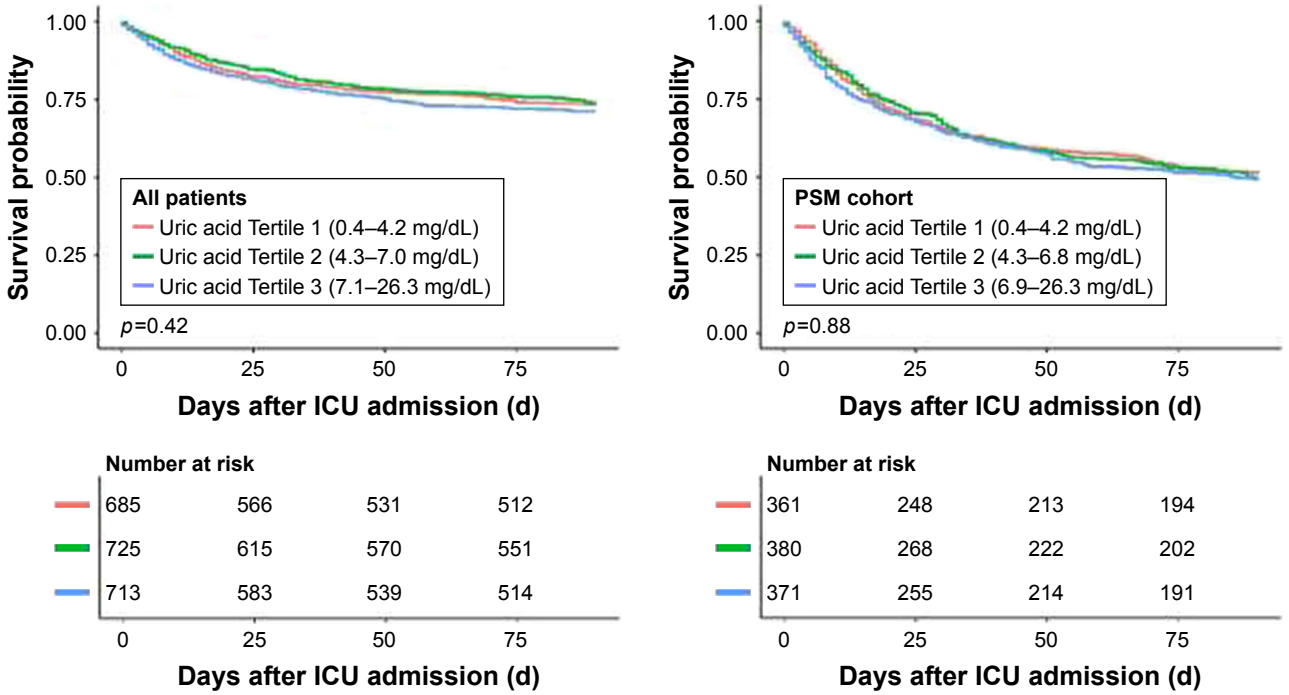

Figure 2 Kaplan–Meier survival curve by different levels of uric acid of all patients and PSM cohort.
Abbreviations: ICU, intensive care unit; PSM, propensity score matching.

hypertension.[21] 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.[22] Ergun et al reported that high serum uric acid levels are predictive for not only long-term mortality but also for short-term mortality.[23] 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.[12–14] 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

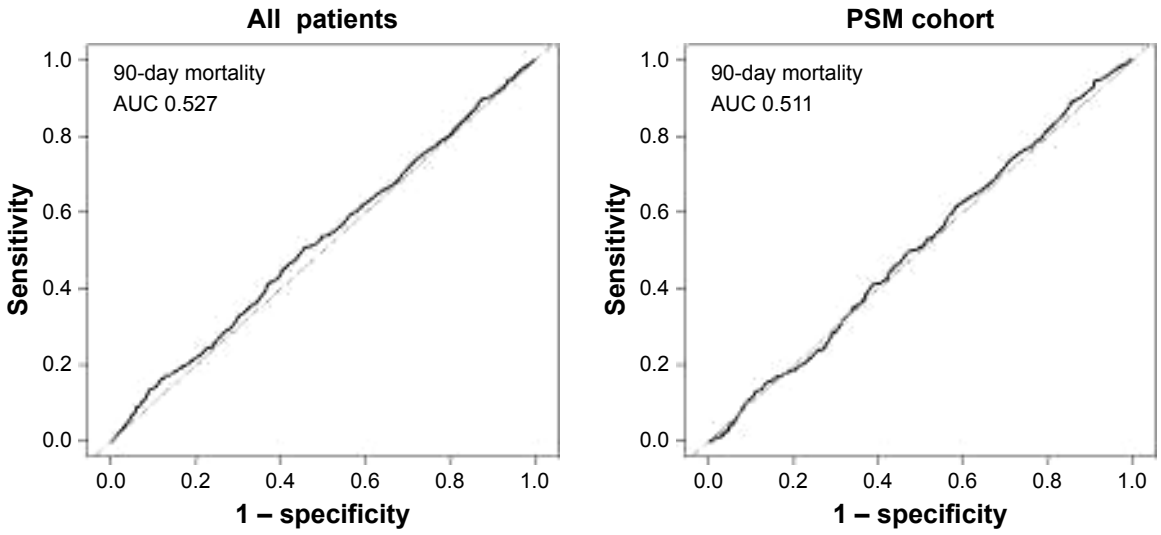

Figure 3 (*Continued*)

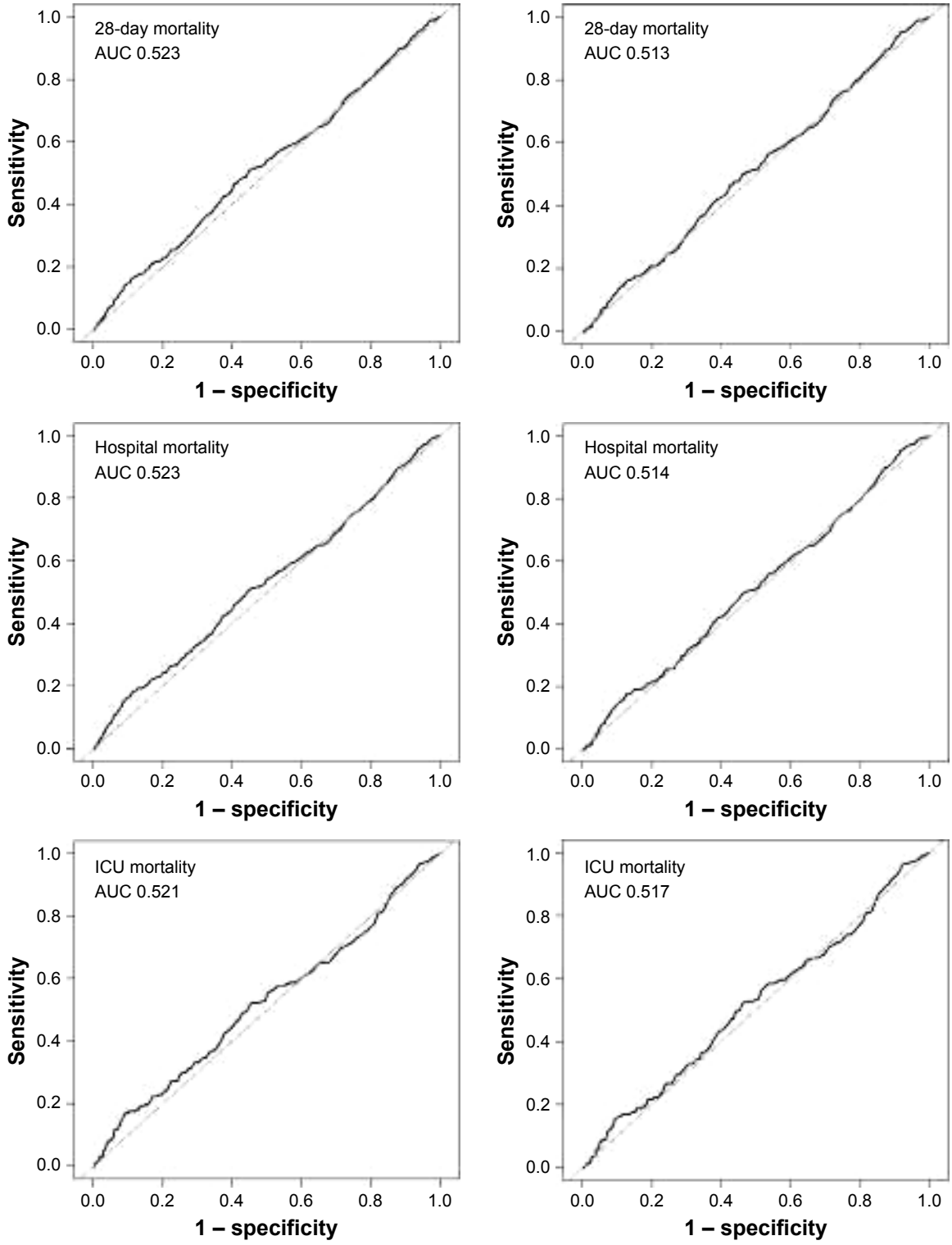

Figure 3 ROC curves of admission serum uric acid for prediction of clinical outcomes in all patients and the PSM cohort.
Abbreviations: ROC curves, receiver operating characteristic curves; ICU, intensive care unit; AUC, area under the ROC curves; PSM, propensity score matching.

serum uric acid and 90-day mortality for 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.

many variables known to affect the outcomes, unmeasured confounders may have affected our results. As we know, the reference value of serum uric acid is different between male and female; hence, gender must be considered in the K-M survival curves. In fact, the results were consistent even after grouped by sex (data not shown), but there were still other potential confounders such as renal replacement therapy on the first day, fluid and electrolyte disorders, which made it difficult to take all these confounders into consideration in the K-M curves. And since there were too many specific primary diagnoses for all the patients, we categorized the primary diseases as several comorbidities (Tables 1 and 2) to make it easier to adjust and analyze. However, it was indisputable that some unmeasured confounders such as gout, uremia, and other uric acid metabolic disorder might still have affected the results. In addition, as a retrospective database study, it was difficult to account for the potential effect of therapy before ICU admission on serum uric acid levels, because such information was usually not documented. Thus, further well-designed prospective study is needed to confirm our results. Second, the present study included data from only one ICU center, which might limit the external applicability of the study results. Third, we found no association between serum uric acid on admission and long-term outcomes of critically ill patients, but whether the changes of serum uric acid would be associated with the clinical outcomes of the patients remained unknown.

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.

Acknowledgments

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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

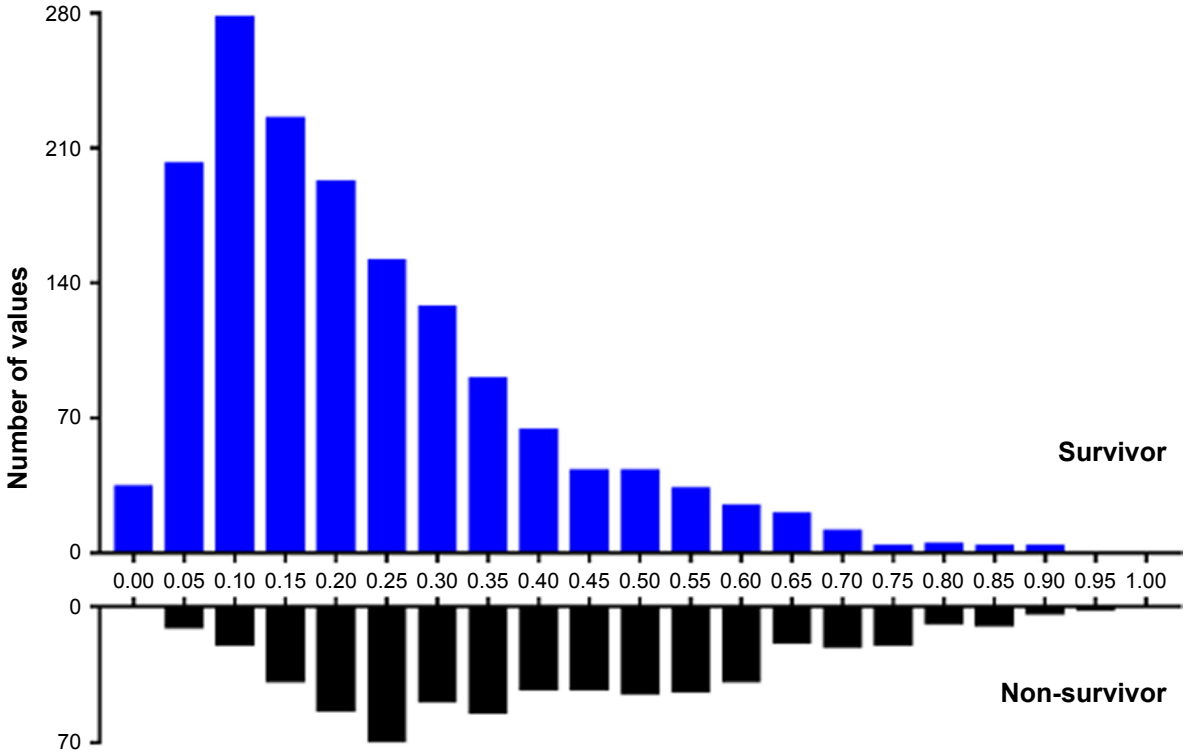

Figure S1 Distribution of propensity scores.

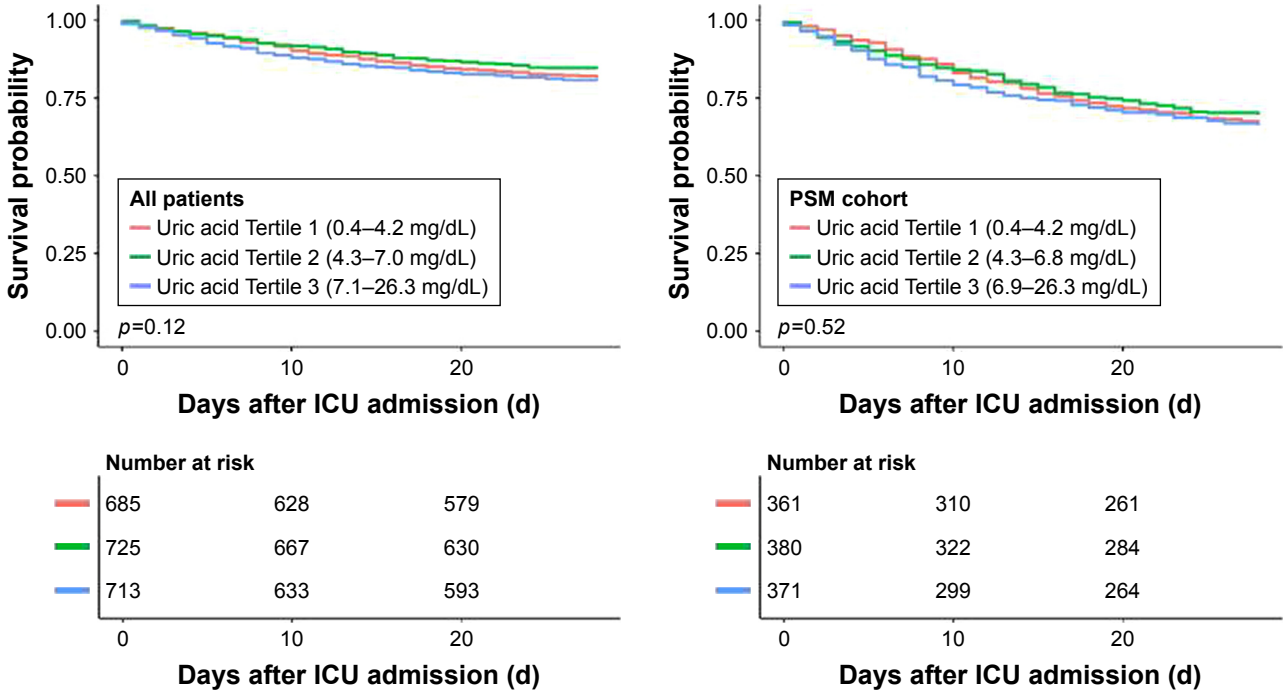

Figure S2 Kaplan–Meier survival curve of 28-day mortality.
Abbreviations: ICU, intensive care unit; PSM, propensity score matching.

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
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

	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
Liver disease			
No	1.0		
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.