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Uric Acid and Acute Kidney Injury in the Critically Ill

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Re: Manuscript KIDNEYMED-D-18-00002R1

Dear Members of the Editorial Board:

Thank you for the review dated December 26th, 2018 and invitation for revision on the above referenced manuscript in *Kidney Medicine*.

We are highly appreciative of the editors' and reviewers' time, effort, thoughtful comments, criticisms, and suggestions. We have attempted to appropriately address the issues raised by the Statistical Editor in the revised manuscript as requested in track changes mode. A 'clean' version of the manuscript is also attached.

A detailed account of the revisions and clarifications (in blue) are below. We hope that the revised manuscript will be found acceptable.

Statistical Editor's Requests:

1. The IRR term should be replaced with relative number of days as the outcome is RRT-free days and the anti-log of the parameter estimate should give the relative number of days and not an incidence rate ratio.

Thank you for this suggestion. We have replaced the IRR term with 'relative number of RRT-free days'. For reference, we also show the parameter estimates from the negative binomial model (below).

Outcome	Unadjusted Parameter Estimate (95% CI)	P	Adjusted* Parameter Estimate (95% CI)	P
RRT-free days	0.11 (-0.36, 0.58)	0.65	0.07 (-0.40, 0.54)	0.77

*Adjusted for age, randomization arm (high vs less intensity), natural log urine output, BUN at enrollment, APACHE II score, and SOFA cardiovascular score

2. In the online supplementary material, on the first page, the table numbering is incorrect.

We have corrected the table numbering in the supplementary material.

3. In the results: "and had lower urine volume" should be replaced with "higher urine volume".

We have made this change.

4. In the results: In the ICU cohort, 40 (19.3%), this percent should be 19.2%.

We have made this change.

5. In the results: the adjusted odds ratio for upper 95% CI for ATN cohort for 28d mortality should be 1.88 and not 1.65.

We have made this change.

6. Please include a row for uric acid in tables 1 and 2.

We have included a row for plasma uric acid in tables 1 and 2.

7. Regarding etiology of AKI for ICU cohort, the data should be shown only for AKI group and so the denominator should be the total AKI in current table 1 and indicated as a footnote (please provide n for AKI per tertiles of uric acid). In online supplementary table 1, please keep the rows for this variable in the total column as "-".

In the revised Table 1, we now include the total number of AKI with frequency in the 'All patients' column and the total number of incident AKI for each tertile with their respective frequencies. The AKI etiologies are now presented as n with respective frequency of the total AKI episodes for 'All patients' and for each tertile. We

have also altered the footnote to show this. In Table S1, we have kept the rows for AKI etiology as '-' in the 'All patients' column as suggested.

Uric Acid and Acute Kidney Injury in the Critically Ill

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Abstract

Rationale & Objective

Uric acid is excreted by the kidney and accumulates in acute kidney injury (AKI). Whether higher plasma uric acid predisposes to AKI or its complications is not known.

Study Design

Prospective observational cohort study.

Setting & Participants

Two independent cohorts of critically ill patients: 1) 208 patients without AKI admitted to the intensive care unit (ICU) at Brigham & Women's Hospital between October 2008 and December 2016; and 2) 250 participants with AKI requiring renal replacement therapy (RRT) who had not yet initiated RRT enrolled in the Acute Renal Failure Trial Network (ATN) study.

Exposure

Plasma uric acid upon ICU admission and prior to RRT initiation in the ICU and ATN study cohorts, respectively.

Outcomes

Incident AKI and 60-day mortality in the ICU and ATN study cohorts, respectively.

Analytical Approach

Logistic regression models were used to test the association of plasma uric acid with incident AKI and 60-day mortality.

Results

In the ICU cohort, median plasma uric acid level was 4.7 mg/dl interquartile range (IQR) [3.6–6.4], and 40 patients (19.2%) developed AKI. Higher plasma uric acid levels associated with incident AKI, but this association was confounded by serum creatinine and was not significant after multivariable adjustment

(adjusted OR per doubling of uric acid 1.50, 95% CI 0.80, 2.81). In the ATN study cohort, median plasma uric acid level was 11.1 mg/dl [8.6–14.2] and 125 participants (50.0%) died within 60 days. There was not a statistically significant association between plasma uric acid levels and 60-day mortality in either unadjusted models or after multivariable adjustment for demographic, severity of illness, and kidney-specific covariates (adjusted OR per doubling of uric acid 1.15, 95% CI 0.71, 1.86).

Limitations

Heterogeneity of ICU patients

Conclusions

Plasma uric acid levels upon ICU admission or prior to RRT initiation are not independently associated with adverse clinical outcomes in critically ill patients.

Summary

Acute kidney injury is a devastating problem in critically ill patients that is associated with increased morbidity and mortality. We evaluated whether higher levels of plasma uric acid were associated with development of acute kidney injury or its complications in two independent cohorts of critically ill patients: 1) patients admitted to the intensive care unit without acute kidney injury and 2) critically ill patients with acute kidney injury requiring renal replacement therapy. We were unable to identify a significant association between higher levels of plasma uric acid with the development of acute kidney injury or mortality in critically ill patients.

Introduction

Acute kidney injury (AKI) is estimated to occur in up to 60% of critically ill patients.[1-3] Patients suffering from AKI in the intensive care unit (ICU) carry a mortality risk of 20-50% and patients with severe AKI requiring renal replacement therapy (AKI-RRT) have a mortality risk of 40-80%.[2,4-6] Renal recovery (no longer requiring RRT) can occur in up to 50% of patients, but the probability of recovery is difficult to assess.[7,8] The pathogenesis of AKI-RRT and mechanisms for recovery are incompletely understood.

Elevations in plasma uric acid (hyperuricemia) are common in patients with impaired kidney function from chronic kidney disease (CKD) and AKI. Multiple studies have found associations between higher levels of uric acid and increased risk for the development of chronic systemic illnesses such as hypertension,[9] cardiovascular disease,[10,11] and chronic kidney disease (CKD).[12,13] Prior studies have demonstrated higher levels of uric acid as a risk factor for the development of contrast-induced AKI[14,15] and AKI after cardiac surgery.[16-19] Few studies have investigated the potential role of uric acid in inciting or perpetuating AKI in critically ill patients. In the setting of AKI from tumor lysis syndrome, hyperuricemia is thought to cause kidney injury by intra-tubular obstruction and intra-renal inflammation by the precipitated crystals.[20-22] Mechanisms beyond tubular obstruction are also potential contributors. In animal models, increased uric acid may lead to endothelial dysfunction,[23,24] renin-aldosterone system (RAS) activation,[25] and oxidative stress.[26]

Little is known about the role of uric acid in AKI outside of tumor lysis syndrome. We wished to test the hypothesis that higher circulating levels of uric acid are a risk factor for the development of AKI and its prognosis. To do so, we measured plasma uric acid levels in stored samples from 2 patient cohorts: 1) critically ill patients admitted to the ICU; and 2) patients with AKI-RRT enrolled into a randomized controlled trial of RRT intensity.

Materials and Methods

Study Design and Population

We conducted a prospective study of the association between plasma uric acid levels and adverse clinical outcomes in 2 independent cohorts of critically ill patients. The first was a prospective observational cohort study and biorepository of patients admitted to the intensive care unit (ICU) at Brigham & Women's Hospital (BWH) between October 2008 and December 2016. This cohort is comprised of patients admitted to the medical and surgical ICUs at BWH as well as patients enrolled in the Registry of Critical Illness (ROCI) cohort study[27] from the medical ICUs at BWH (collectively named ICU cohort). The second was the Veterans Affairs (VA)/National Institutes of Health Acute Renal Failure Trial Network (ATN) study, a multicenter, randomized clinical trial of intensive versus less intensive RRT that enrolled critically ill patients between November 2003 and July 2007.[28] All participants provided written informed consent for biomarker measurements. The study protocol was approved by the Partners Human Research Committee (the BWH Institutional Review Board: 2007P000894 and 2016P001542), and is in accordance with the principles of the Declaration of Helsinki.

Enrollment Criteria, Study Procedures, Selection of Time Points, and Data Collection

Inclusion criteria for the ICU cohort were age ≥18 years and admission to a medical or surgical ICU with blood samples available within 72h of arrival to the ICU. Exclusion criteria were: (1) current receipt of RRT, (2) anticipated ICU stay <48h, (3) admission to the ICU for a low-risk condition such as airway monitoring or serial neurologic checks, (4) pregnancy, or (5) enrollment in a conflicting research study. ICU patients were screened and enrolled intermittently through the study period. 128 patients were eligible from the medical and surgical ICUs at BWH and 120 patients were eligible from the ROCI cohort. Since worsening kidney function can increase plasma uric acid levels, we adjudicated the medical record of each potentially eligible patient and excluded anyone with clinical evidence of AKI upon study enrollment based on serum creatinine (SCr) values. Eligible patients with a rising SCr prior to or upon study enrollment who met criteria for AKI were excluded. Patients with an elevated SCr value without prior values were excluded if they experienced improvement in SCr to a nadir level that would have qualified them to meet criteria for AKI. We excluded 40 patients from the medical/surgical ICUs at BWH and ROCI cohort due to clinical evidence of AKI upon study enrollment, which

resulted in 208 patients in the ICU cohort. We obtained baseline demographic information, co-morbidities, and severity of illness upon enrollment assessed by the Acute Physiology and Chronic Health Evaluation (APACHE II) score.[29] All patients were followed until hospital discharge, death, or day 28 after enrollment, whichever occurred first.

The ATN study was an interventional trial of higher vs lower intensity RRT that included critically ill patients diagnosed with AKI-RRT with failure of at least one non-renal organ system or sepsis. The study excluded patients with: (1) CKD (defined as pre-morbid SCr >2 mg/dl in men and >1.5 mg/dl in women), (2) AKI clinically believed to be due to an etiology other than acute tubular necrosis, (3) prior kidney transplantation, and (4) comfort measures only status. Full inclusion and exclusion criteria for the ATN study are described elsewhere.[28] Among the 1124 ATN study participants, blood samples were collected in 817 participants. Since receipt of RRT would lower plasma uric acid levels, we excluded 561 participants who received some form of RRT prior to randomization. Of the remaining samples, 6 were deemed unsatisfactory for measurement, resulting in 250 individuals for inclusion in this study. We obtained baseline characteristics including demographic information along with other pertinent clinical and laboratory data upon enrollment in the ATN study. Severity of illness was obtained upon enrollment using the APACHE II score and Sequential Organ Failure Assessment (SOFA) cardiovascular score. In the ATN study, all participants were followed daily until hospital discharge, death, or day 28 after randomization, whichever occurred first. Outcomes were ascertained daily during hospitalization and at day 60 and 1-year using telephone and/or mail follow-up.

Blood sample collection and laboratory assays

In the ICU cohort, blood samples were collected in EDTA-containing vacutainers and were processed, aliquoted, and stored at -80°C within 4 hours of collection. In the ATN study, blood samples were collected and immediately placed on ice and centrifuged at 4°C. They were separated into aliquots, and stored frozen (-20°C) at the collection site until shipment. Batched samples were shipped on dry ice by commercial courier to the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) Core Laboratory at the VA Boston Healthcare System. Samples were then stored at -80°C. Samples were shipped from MAVERIC on dry ice, thawed, and sub-aliquoted into 0.5ml vials. Plasma uric acid measurements for the ICU cohort were performed at the laboratories of University of Washington (n=115) and BWH (ROCI, n=93). ATN study samples

were processed at the University of California San Diego. All uric acid assays were performed using the colorimetric peroxidase-coupled indirect equilibrium uricase method. The interassay coefficients of variation at each laboratory was <10%.

Clinical Outcomes

Authors AS, RP, DEL, and AH adjudicated outcomes by reviewing the medical record while still blinded to study measurements in the ICU cohort. The pre-specified primary outcome was incident AKI (occurring after enrollment/arrival to the ICU). The secondary outcome was 90-day mortality. AKI was defined according to the SCr-based criteria established by the Kidney Disease Improving Global Outcomes Work Group.[30] Incident AKI was defined as ≥0.3 mg/dl increase in enrollment SCr over any 48-hour time period during the first 7 days in ICU, or an increase in SCr ≥1.5 times enrollment SCr within 7 days. AKI stage was defined as follows: stage 1, increase in SCr 1.5–1.9 times enrollment SCr or absolute increase ≥0.3 mg/dl; stage 2, increase in SCr 2.0–2.9 times enrollment SCr; and stage 3, increase in SCr ≥3.0 times enrollment, an absolute increase in SCr ≥0.5 mg/dl to a level ≥4.0 mg/dl, or initiation of RRT. Urine output data were not available in all patients.

In the ATN study cohort, the primary outcome was 60-day mortality. Secondary outcomes were 28-day mortality, duration of RRT (RRT-free days), and recovery of kidney function amongst survivors through day 28. To avoid the competing risk of death, RRT-free days were calculated as 28 minus the number of days requiring RRT assuming survival to 28 days. Any participant who died before 28 days was assigned a score of zero.[31-33]

Statistical Analysis

Descriptive statistics were summarized and presented as frequencies, mean ± standard deviation (SD), or median with interquartile range [IQR]. We assessed all variables for normality and log-transformed as appropriate. Plasma uric acid was examined as a continuous variable (log base 2, so that interpretation would be per doubling of the exposure) and categorized as tertiles. We assessed the association between plasma uric acid levels and 2-group comparisons using the Wilcoxon rank-sum test and Kruskal-Wallis test for multiple group comparisons. We used Spearman correlation to assess the association between plasma uric acid levels and continuous variables. We used Chi-square tests to compare plasma uric acid tertiles with categorical variables, and ANOVA or Kruskal-Wallis tests for normally or non-normally distributed continuous variables,

respectively. To assess for differences between the original ATN study cohort and the subset of patients without RRT prior to randomization, we used t-test for normal continuous data, Wilcoxon rank-sum test for non-normal continuous data, and Chi-square or Fisher exact test for categorical data. We evaluated the predictors of plasma uric acid levels in the ATN study cohort with linear regression.

We fit multivariable logistic regression models to examine associations between plasma uric acid and the dichotomous outcomes of incident AKI, mortality, and renal recovery. Model results are reported as odds ratio (OR) with 95% confidence interval (95% CI). We used a multivariable negative binomial regression model for the outcome of RRT-free days. Model results are reported as ~~incidence rate ratios (IRR)~~relative number of RRT-free days with 95% confidence interval (95% CI). We assessed for confounding by iteratively generating increasingly adjusted models. All comparisons were two-tailed with $P < 0.05$ considered significant. All statistical analyses were performed using SAS software (version 9.4, Cary, NC).

Results

Characteristics of study participants

In the ICU cohort, the mean age was 61.8 ± 15.3 years, 94 (45.2%) were female, and 177 (85.1%) were white. In the ATN study, the mean age was 62.0 ± 14.6 years, 77 (30.8%) were female, and 199 (79.6%) were white. The primary etiology of AKI was multifactorial in 18 of 40 (45.0%) patients with AKI in the ICU cohort and in 135 (54.0%) participants in the ATN study cohort. Additional baseline characteristics for the ICU cohort and ATN study are in **Tables 1 and 2**, respectively. **Tables S1 and S2** show the baseline characteristics for the ICU cohort and ATN study cohort by their primary outcomes, respectively. Compared to the characteristics of the participants in the parent ATN study not included in this study (n=874), the participants in the subcohort with plasma uric acid measurements were older, more commonly white, required less mechanical ventilation, and had ~~lower~~ higher urine volume, ~~but higher~~ BUN, and ~~-~~SCr values prior to RRT initiation (**Table S3**).

Baseline plasma uric acid levels

Median enrollment plasma uric acid level was 4.7 mg/dl with a range of 1.5 – 20.3 mg/dl in the ICU cohort. In the ATN study, the median plasma uric acid level prior to RRT was 11.1 mg/dl with a range of 3.3 – 29.4 mg/dl.

Factors associated with plasma uric acid levels

There were no differences between plasma uric acid levels by sex, race, or ICU setting in the ICU or ATN study cohorts. Plasma uric acid levels were higher in patients with a history of diabetes mellitus (6.4 [4.2 – 9.2] vs 4.5 [3.5 – 6.0] mg/dl, $P < 0.001$) and congestive heart failure (8.0 [5.4 – 10.0] vs 4.6 [3.6 – 6.3] mg/dl, $P = 0.007$) in the ICU cohort. Plasma uric acid had a positive correlation with APACHE II scores in the ICU cohort ($r_s = 0.19$, $P = 0.007$). In the ATN study cohort, there were no significant differences in plasma uric acid levels by treatment arm, SOFA cardiovascular score, or by presence of oliguria. Age was associated with plasma uric acid levels in the ICU cohort ($r_s = 0.19$, $P = 0.006$) and the ATN study participants ($r_s = -0.13$, $P = 0.03$). In the ICU cohort, plasma uric acid positively correlated with enrollment SCr ($r_s = 0.36$, $P < 0.001$). In the ATN study cohort, plasma uric acid had a positive correlation with enrollment BUN ($r_s = 0.22$, $P < 0.001$), enrollment SCr ($r_s = 0.29$, $P < 0.001$), and change in SCr from admission to enrollment ($r_s = 0.25$, $P < 0.001$). **Figure 1**

demonstrates the correlation between enrollment SCr and plasma uric acid in both cohorts. **Table S4** demonstrates unadjusted determinants of plasma uric acid levels in the ATN study cohort.

Association of plasma uric acid with study outcomes

In the ICU cohort, 40 (19.23%) patients developed AKI (52.5% had stage 2 or 3), and 52 (25.0%) patients reached the secondary outcome of 90-day mortality. Plasma uric acid levels were higher upon enrollment in patients who developed AKI compared to patients who did not (5.7 [4.1 – 7.8] vs 4.6 [3.5 – 6.2] mg/dl, P=0.03) (**Figure 2**). In the ATN study cohort, 125 (50.0%) participants died at 60 days, 108 (43.2%) participants died at 28 days, and 65 (26.0%) participants who survived to day 28 experienced renal recovery. The mean number of RRT-free days was 6.7 ± 8.9. There were no differences in mortality or renal recovery by tertiles of plasma uric acid levels (**Figure 3**). **Table 3** and **Table 4** demonstrate the unadjusted and adjusted associations of plasma uric acid with the renal and mortality outcomes, respectively.

In the ICU cohort, higher levels of plasma uric acid were associated with incident AKI (OR 1.78, 95% CI 1.03, 3.05) but not 90-day mortality in unadjusted analyses (OR 1.16, 95% CI 0.72, 1.87). After multivariable adjustment for age, diabetes mellitus, APACHE II score, and enrollment SCr, plasma uric acid was no longer associated with incident AKI (adjusted OR 1.50, 95% CI 0.80, 2.81). Adjustment for enrollment SCr alone was sufficient to render the association non-significant (adjusted OR 1.49, 95% CI 0.83, 2.66).

In the ATN study cohort, plasma uric acid levels were not associated with the primary outcome of 60-day mortality in unadjusted models. Adjustment for age, randomization arm (intensive vs less intensive RRT), urine output, enrollment BUN, SOFA cardiovascular score, and APACHE II score did not change the association with 60-day mortality (adjusted OR 1.15, 95% CI 0.71, 1.86). Similarly, there was no association between plasma uric acid levels and 28-day mortality (adjusted OR 1.16, 95% CI 0.72, 1.8865), renal recovery (adjusted OR 1.05, 95% CI 0.54, 2.04) amongst survivors through day 28, or change in RRT-free days (IRR 1.07 95% CI 0.67, 1.72) after multivariable adjustment. Substitution of eGFR for SCr in the multivariable adjustment did not fundamentally change the results for either cohort.

Discussion

In this study involving 2 cohorts of critically ill patients, we were unable to identify an association between uric acid levels and subsequent risk of AKI or its complications. In the ICU cohort, higher levels of plasma uric acid were associated with incident AKI in unadjusted models, but this effect was attenuated and no longer significant after multivariable adjustment. We found no statistically significant association between plasma uric acid upon admission to the ICU and 90-day mortality. In the ATN study, there was no statistically significant association between plasma uric acid and mortality, renal recovery, or duration of RRT in individuals with AKI-RRT.

Our results do not support the hypothesis that uric acid predisposes to AKI in ICU patients or mortality in patients with established severe AKI. Preclinical evidence in favor of this hypothesis derives from both in vitro and in vivo studies, which established several potential mechanisms of kidney injury from uric acid, including afferent arteriole vasoconstriction,[34,35] decreased renal blood flow due to endothelial dysfunction, oxidative stress,[36-38] and augmentation of the inflammatory response.[34] Our results also conflict with a number of published studies on the association between uric acid and the development of AKI or risk of death.[39] Higher uric acid levels have been reported to predict the risk of AKI in hospitalized patients[40-42] as well as after cardiac surgery,[16-18] with some reports of a J-shaped association showing higher risk at both very low and high levels of uric acid.[43] In the Atherosclerosis Risk in Communities study, higher uric acid levels predicted the risk of a hospital stay with AKI over a mean follow-up time of 12 years, although results from Mendelian randomization analyses did not support a causal association.[44] Prior retrospective studies in cardiac surgery have found an increased risk for post-operative AKI in patients with higher pre-operative uric acid levels.[16,17,43] However, these prior studies in cardiac surgery adjust for kidney function as a dichotomous variable (eGFR < 60 ml/min/1.73m^2), whereas adjustment as a continuous variable may address confounding by kidney function more appropriately. A recent prospective study in 247 patients undergoing cardiac surgery demonstrated that patients with pre-operative uric acid levels ≥373 μmol/l (6.3 mg/dl) were at >5-fold increased risk for development of post-operative AKI even after adjustment for pre-operative serum creatinine. However, this cohort had a relatively low event-rate (12.1%) and also had limited power for the multivariable analysis.[18] A prior prospective study of 144 critically ill patients suggested that higher levels of plasma uric acid were

associated with a secondary outcome of incident AKI by univariate analysis, but it is not clear whether individuals already had AKI upon ICU admission.[42]

Our prospective study investigated whether higher levels of plasma uric acid increased the risk for development of AKI and mortality in high-risk critically ill patients admitted to the ICU. We measured plasma uric acid within 72 hours of ICU admission in the ICU cohort and adjudicated the medical records to exclude patients with clinical evidence of AKI upon enrollment to reduce confounding by already worsening GFR in the setting of AKI. Despite reasonably well preserved kidney function upon enrollment, the association of plasma uric acid with incident AKI was still confounded by SCr.

To our knowledge, this is the first study to evaluate the association of plasma uric acid with mortality, renal recovery, and duration of RRT in patients with severe AKI requiring RRT. Few studies have evaluated the association of uric acid with mortality in critically ill patients. In a study of 1140 consecutive patients undergoing coronary artery bypass grafting, Hillis et al. found a 1.5-fold increased risk of all-cause mortality per 1.68 mg/dl increase in uric acid over a median follow-up of 4.5 years.[45] In the ATN study cohort, plasma uric acid levels were significantly higher than the normal range. Despite the atypically high levels of plasma uric acid and high event rates, we did not detect an association between plasma uric acid and the study outcomes even in unadjusted models. Severe AKI likely accounts for the high plasma uric acid levels, but a high inflammatory or hypercatabolic state in critically ill patients could also have contributed.

A recent scientific workshop reviewed the existing evidence for the association between uric acid and adverse outcomes in CKD and AKI. They suggested there was insufficient evidence to recommend routine treatment of asymptomatic hyperuricemia in patients with hypertension, kidney disease, or diabetes mellitus to reduce the risk of AKI. The authors also called for more evidence from well-designed adequately powered clinical trials.[46] Two small studies tested whether lowering plasma uric acid may be beneficial in reducing the risk of AKI after cardiac surgery, and found no benefit when treated with pre-operative allopurinol plus vitamin E or rasburicase (recombinant uricase), respectively.[47,48]

We acknowledge this study has several limitations. The single center recruitment in the ICU cohort, heterogeneity of ICU patients, and lack of racial diversity in both cohorts limit the generalizability of the study results to all critically ill patients. We were unable to account for volume overload in our studies, which could

dilute plasma uric acid levels. This may have been most pertinent in the ATN study cohort as patients with AKI-RRT may develop volume overload with declining urine output. In addition, the modest sample size may have led to wide confidence intervals around the point estimates for the study outcomes, which did not reach significance. Therefore, we cannot exclude the possibility that we were unable to detect a potentially meaningful association between higher levels of plasma uric acid and adverse clinical outcomes.

In summary, higher levels of plasma uric acid measured in critically ill patients upon ICU admission and prior to RRT initiation were not observed to be statistically associated with development of AKI or adverse clinical outcomes after AKI-RRT, respectively.

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We thank the Acute Renal Failure Trial Network (ATN) Study Investigators and the National Institute of Diabetes and Digestive Diseases (NIDDK) data repository for the data used in this study. We are grateful to the following members of the Registry of Critical Illness (ROCI) who helped assemble this cohort: Dr. Paul Dieffenbach, Dr. Samuel Ash, Dr. Laura Fredenburgh, and Dr. Joshua Englert. We thank the invaluable work of the members of the Waikar Lab group at BWH.

The ATN Study was performed by the ATN Study investigators and supported by the Cooperative Studies Program of the Department of Veterans Affairs (VA) Office of Research and Development and the NIDDK. This paper does not necessarily reflect the opinions or views of the ATN Study investigators, VA, or NIDDK. The funders of this study had no role in the study design, collection, analysis, interpretation of data, drafting of the manuscript, or decision to submit the manuscript for publication.

Part of this work was presented as a poster at the American Society of Nephrology Scientific Session in November 2016.

Conflict of Interest Statement:

AS has been a consultant for Horizon Pharma. PMP has been a consultant for GE Healthcare, Baxter, Novartis, Healthspan Dx, and Durect. SSW received consulting fees for serving on the data safety monitoring board for Takeda, for trials involving uric acid lowering agents. The authors declared no other relevant conflicts of interest.

Author Contributions:

Study design: AS, SSW; data acquisition: all authors; data analysis: AS, SSW; data interpretation: all authors. Each author also contributed important intellectual content during manuscript drafting or revision and ensured that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Table 1. Baseline Characteristics of the ICU Cohort by Uric Acid Tertiles

Characteristic	All patients* (n=208)	Tertile 1: 1.5 – 3.9 mg/dl (n=67)	Tertile 2: 4.0 – 5.8 mg/dl (n=72)	Tertile 3: 5.9 – 20.3 mg/dl (n=69)
Plasma uric acid*, mg/dl	4.7 [3.6 – 6.4] (1.5 – 20.3)	1.5 – 3.9	4.0 – 5.8	5.9 – 20.3
Demographics				
Female, n (%)	94 (45.2)	26 (38.8)	35 (48.6)	33 (47.8)
Age, years	61.8 ± 15.3	57.6 ± 15.4	63.4 ± 15.3	64.2 ± 14.4
White, n (%)	177 (85.1)	61 (91.0)	61 (84.7)	55 (79.7)
Enrollment Characteristics				
SCr, mg/dl	0.8 [0.6 – 1.0]	0.7 [0.5 – 0.8]	0.8 [0.6 – 1.0]	0.9 [0.8 – 1.1]
eGFR, ml/min/1.73m^2	91.1 ± 26.6	102.2 ± 23.6	90.4 ± 26.1	81.1 ± 26.0
APACHE II	17 [12 – 24]	16 [11 – 22]	16 [12 – 23]	18 [13 – 27]
Sepsis, n (%)	113 (54.3)	42 (62.7)	30 (41.7)	41 (59.4)
AKI Etiology[a], n (%)	40 (19.2)	9 (13.4)	12 (16.7)	19 (27.5)
Multifactorial	18 (45.08.7)	2 (22.23.0)	6 (50.08.3)	10 (52.614.5)
Ischemic	9 (22.54.3)	2 (22.23.0)	3 (25.04.2)	4 (21.05.8)
Pre-renal	6 (15.02.9)	3 (33.34.5)	2 (16.72.8)	1 (5.31.5)
Sepsis	5 (12.52.4)	2 (22.23.0)	1 (8.31.4)	2 (10.52.9)
Other	2 (5.01.0)	0 (0)	0 (0)	2 (10.52.9)
Co-morbid Conditions, n (%)				
Active malignancy	84 (40.4)	28 (41.8)	32 (44.4)	24 (34.8)
Chronic lung disease	49 (23.6)	14 (20.9)	16 (22.2)	19 (27.5)
Diabetes mellitus	44 (21.2)	8 (11.9)	10 (13.9)	26 (37.7)
Congestive heart failure	12 (5.8)	2 (3.0)	2 (2.8)	8 (11.6)
Chronic liver disease	10 (4.8)	4 (6.0)	3 (4.2)	3 (4.4)
ICU type, n (%)				
Medical	112 (53.9)	26 (38.8)	37 (51.4)	49 (71.0)
Surgical	96 (46.1)	41 (61.2)	35 (48.6)	20 (29.0)

Data presented as mean ± standard deviation (SD), or median with interquartile range [IQR] for continuous variables and frequencies for binary or categorical variables. Estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration equation.

*Plasma uric acid presented as median [IQR] with range for all patients and range for each tertile.Median plasma uric acid 4.7 [3.6 – 6.4] mg/dl

[a]KDIGO stage 1 AKI or greaterPercentages are per total KDIGO stage 1 AKI or greater in all patients and per tertile

Abbreviations: AKI, acute kidney injury; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; ICU, intensive care unit

Table 2. Baseline Characteristics of ATN Study Participants by Uric Acid Tertiles

Characteristics	All participants* (n=250)	Tertile 1: 3.3 – 9.4 mg/dl (n=83)	Tertile 2: 9.5 – 12.9 mg/dl (n=83)	Tertile 3: 13 – 30 mg/dl (n=84)
Plasma Uric Acid*, mg/dl	11.1 [8.6 – 14.2] (3.3 – 29.4)	3.3 – 9.4	9.5 – 12.9	13.0 – 29.4
Demographics				
Female, n (%)	77 (30.8)	31 (37.4)	25 (30.1)	21 (25.0)
Age, years	62.0 ± 14.6	65.5 ± 13.1	60.5 ± 15.7	59.9 ± 14.5
White, n (%)	199 (79.6)	67 (80.7)	67 (80.7)	65 (77.4)
Pre-morbid Characteristics				
SCr, mg/dl	1.1 [0.8 – 1.4]	1.0 [0.8 – 1.3]	1.1 [0.8 – 1.4]	1.1 [0.9 – 1.4]
eGFR, ml/min/1.73m^2	69.1 ± 32.8	72.1 ± 32.7	68.5 ± 33.7	66.8 ± 32.3
Weight, kg	76.4 ± 15.6	73.1 ± 17.3	76.5 ± 13.4	79.5 ± 15.4
Co-morbid Conditions[a], n (%)				
Cardiovascular disease	82 (32.8)	30 (36.1)	21 (25.3)	31 (36.9)
Diabetes Mmellitus	72 (28.8)	20 (24.1)	23 (27.7)	29 (34.5)
Malignancy	50 (20.0)	15 (18.1)	17 (20.5)	18 (21.4)
Immunocompromised	35 (14.0)	11 (13.3)	11 (13.3)	13 (15.5)
Cerebrovascular disease	29 (11.6)	8 (9.6)	9 (10.8)	12 (14.3)
Chronic Hhypoxemia	25 (10.0)	11 (13.3)	4 (4.8)	10 (11.9)
Enrollment Characteristics				
BUN prior to RRT, mg/dl	69.5 ± 30.1	62.8 ± 31.3	67.1 ± 26.5	78.5 ± 30.3
SCr prior to RRT, mg/dl	4.1 [3.0 – 5.6]	3.6 [2.7 – 4.7]	4.2 [3.1 – 5.4]	4.7 [3.7 – 6.3]
MAP, mmHg	76.0 ± 15.4	74.8 ± 15.3	77.7 ± 15.4	75.6 ± 15.5
Urine volume, ml/24 hrs	195 [72 – 545]	155 [70 – 455]	255 [107 – 532]	210 [62 – 638]
Urine volume, ml/hr	10.9 [4.2 – 26.0]	8.1 [4.9 – 19.6]	12.2 [5.3 – 26.3]	10.6 [2.8 – 29.2]
Oliguria, n (%)	189 (75.6)	66 (79.5)	63 (75.9)	60 (71.4)
Mechanical Ventilation, n (%)	189 (75.6)	65 (78.3)	62 (74.7)	62 (73.8)
APACHE II	26 [21 – 31]	25 [21 – 31]	27 [22 – 32]	26 [22 – 31]
SOFA Cardiovascular, n (%)				
0-2	102 (40.8)	30 (36.1)	34 (41.0)	38 (45.2)
3-4	148 (59.2)	53 (63.9)	49 (59.0)	46 (54.8)
Treatment, n (%)				
Intensive	122 (48.8)	45 (54.2)	35 (42.2)	42 (50.0)
Less-intensive	128 (51.2)	38 (45.8)	48 (57.8)	42 (50.0)
ICU type, n (%)				
Medical	122 (48.8)	36 (43.4)	43 (51.8)	43 (51.2)
Surgical	108 (43.2)	38 (45.8)	35 (42.2)	35 (41.7)
Other	20 (8.0)	9 (10.8)	5 (6.0)	6 (7.1)
Post-surgical, n (%)	126 (50.4)	47 (56.6)	43 (51.8)	36 (42.9)
Etiology of AKI[b], n (%)				
Ischemic	198 (79.2)	66 (79.5)	66 (79.5)	66 (78.6)
Nephrotoxic	48 (19.2)	16 (19.2)	15 (18.1)	17 (20.2)
Sepsis	132 (52.8)	41 (49.4)	49 (59.0)	42 (50.0)
Multifactorial	135 (54.0)	39 (47.0)	45 (54.2)	51 (60.7)

Data presented as mean ± SD, or median [IQR] for continuous variables and frequencies for binary or categorical variables. eGFR was determined using the Modification of diet in renal disease (MDRD) equation.
*Plasma uric acid presented as median [IQR] with range for all participants and range for each tertile.Median plasma uric acid level 11.1 [8.6–14.2] mg/dl
[a]Cardiovascular disease includes participants with a history of myocardial infarction, angina, or congestive heart failure. Diabetes mellitus includes participants with a history of end organ disease from diabetes, use of diabetic diet, or on diabetic medications. Malignancy includes participants with a history of leukemia and

tumors with or without metastasis. Immunocompromised includes participants with a history of human immunodeficiency virus, acquired immune deficiency syndrome, or on immunosuppressive therapy. Cerebrovascular disease includes participants with a history of transient ischemic attack or stroke.
[b]Participants could have had more than reason for AKI

Abbreviations: AKI, acute kidney injury; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit

Table 3. Association of Uric Acid with Renal Outcomes in the ICU and ATN Study Cohorts

Outcome	Number of Events	Unadjusted	P	Adjusted	P
ICU					
Incident AKI[+]	40	1.78 (1.03, 3.05)	0.04	1.50 (0.80, 2.81)	0.2
ATN Study					
RRT-free days*	--	1.12 (0.70, 1.79)	0.7	1.07 (0.67, 1.72)	0.8
Renal ~~R~~recovery*	65	1.40 (0.79, 2.47)	0.2	1.05 (0.54, 2.04)	0.9

Plasma uric acid levels are $\log_2$ transformed. Measures of association presented as OR with 95% CI for dichotomous outcomes and ~~incidence rate ratio (IRR)~~ relative number of RRT-free days with 95% CI ~~for RRT-free days~~.

[+]Adjusted for age, diabetes mellitus, APACHE II, and enrollment SCr

*Adjusted for age, randomization arm (high vs less intensity), natural log urine output, BUN at enrollment, APACHE II score, and SOFA cardiovascular score

Abbreviations: ICU, intensive care unit; RRT, renal replacement therapy

Table 4. Association of Uric Acid with Mortality in the ICU and ATN Study Cohorts

Outcome	Events	Unadjusted	P	Adjusted	P
ICU					
90-day mortality[+]	52	1.16 (0.72, 1.87)	0.5	0.98 (0.57, 1.67)	0.9
ATN Study					
60-day mortality*	125	1.04 (0.69, 1.57)	0.9	1.15 (0.71, 1.86)	0.6
28-day mortality*	108	1.09 (0.72, 1.65)	0.7	1.16 (0.72, 1.88)	0.5

Plasma uric acid levels are $\log_2$ transformed. Measures of association presented as OR with 95% CI for dichotomous outcomes.

[+]Adjusted for age, diabetes mellitus, APACHE II, and enrollment SCr

*Adjusted for age, randomization arm (high vs less intensity), natural log urine output, BUN at enrollment, APACHE II score, and SOFA cardiovascular score

Abbreviations: ICU, intensive care unit; RRT, renal replacement therapy

Figure Legends

Figure 1. Association between Plasma Uric Acid and Serum Creatinine

Scatterplots of enrollment plasma uric acid concentrations and their association with enrollment serum creatinine in in the ICU cohort (r_s = 0.36, P < 0.001), and ATN study cohort (r_s = 0.29, P < 0.001).

Figure 2. Scatterplots of Plasma Uric Acid in Patients with and without AKI in the ICU Cohort

Plasma uric acid levels were higher in patients who developed AKI (5.7 mg/dl [4.1 – 7.8]) compared to patients who did not (4.6 mg/dl [3.5 – 6.2]) (P = 0.03).

Figure 3. Association of Plasma Uric Acid levels with Mortality and Renal Recovery in ATN Study Cohort

Unadjusted association between plasma uric acid and adverse clinical outcomes. There were no differences in 60-day mortality, 28-day mortality, or alive with renal recovery through day 28 between the groups. Reference is Tertile 1 and refers to plasma uric acid range: 3.3-9.4 mg/dl; Tertile 2: 9.4-12.9 mg/dl; Tertile 3: 12.9-29.4 mg/dl. For 60-day mortality, Tertile 3: 0.93 (0.51, 1.71), Tertile 2: 0.65 (0.35, 1.19); For 28-day mortality, Tertile 3: 1.03 (0.56, 1.89), Tertile 2: 0.71 (0.38, 1.31); Alive with Renal Recovery, Tertile 3: 1.66 (0.72, 3.86), Tertile 2: 1.47 (0.65, 3.32).

Figure 1

Click here to access/download;Figure;Figure1_UA_ICU_12.17.18_KidMed.pptx

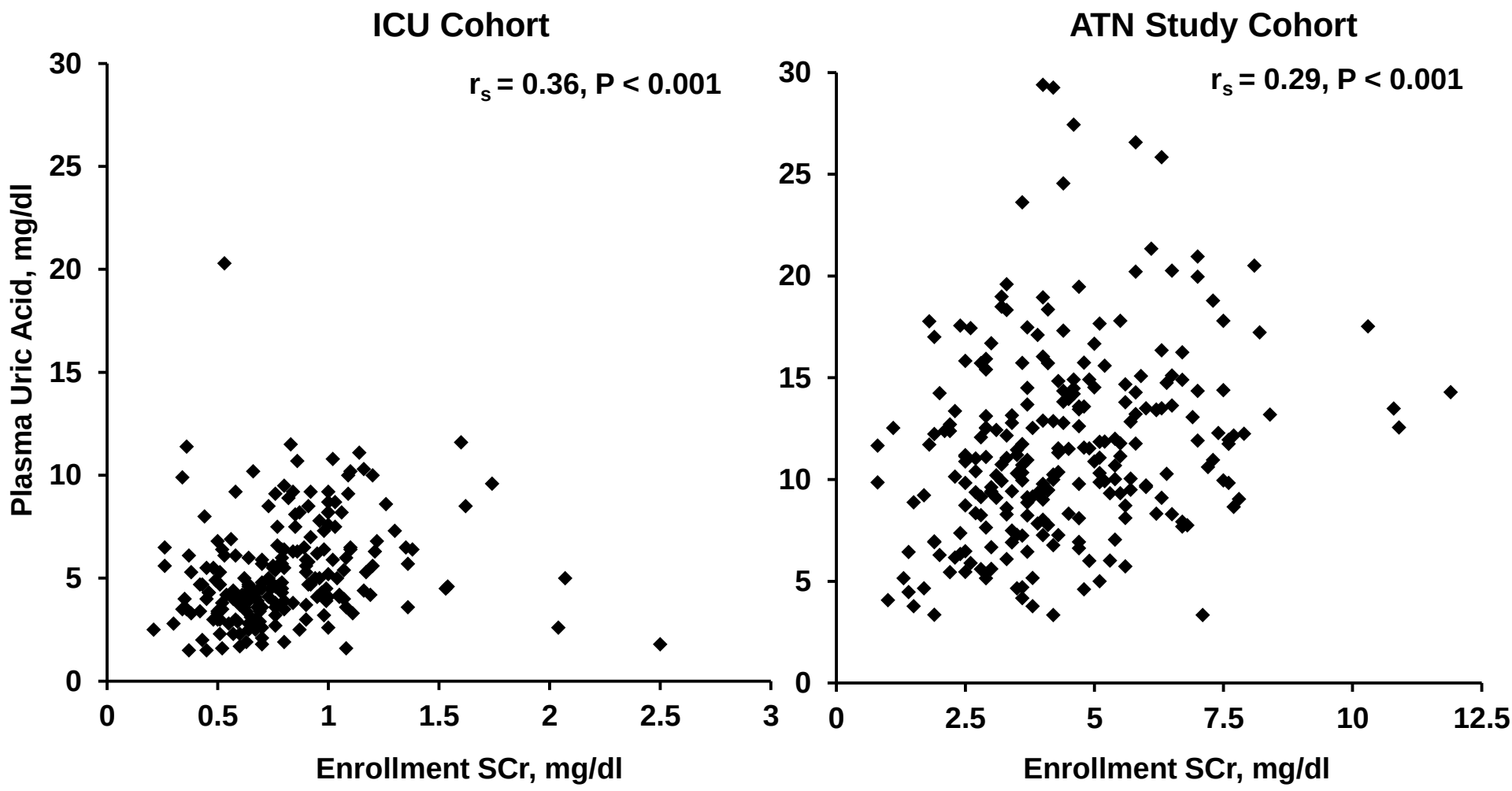

Figure 2

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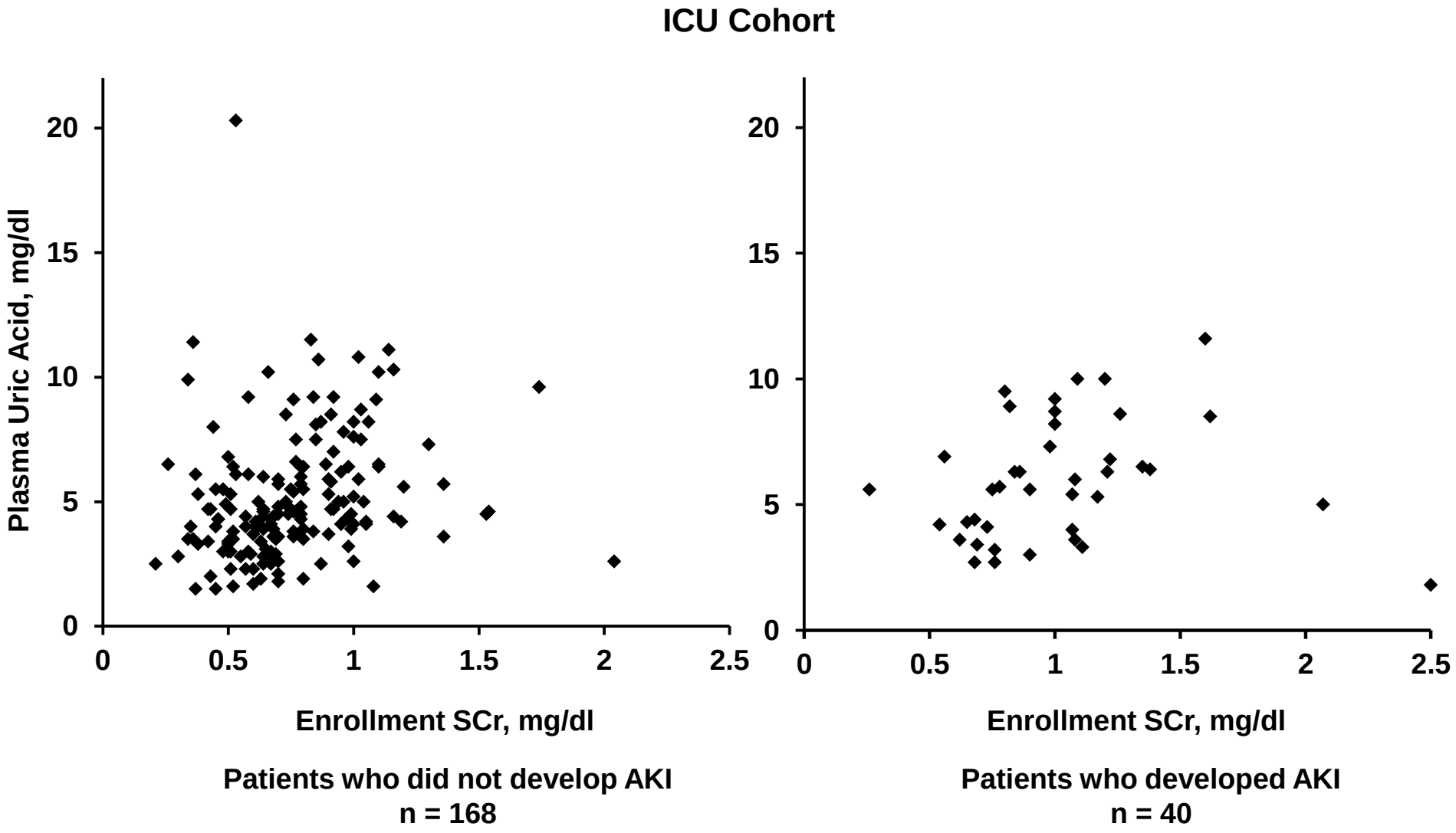
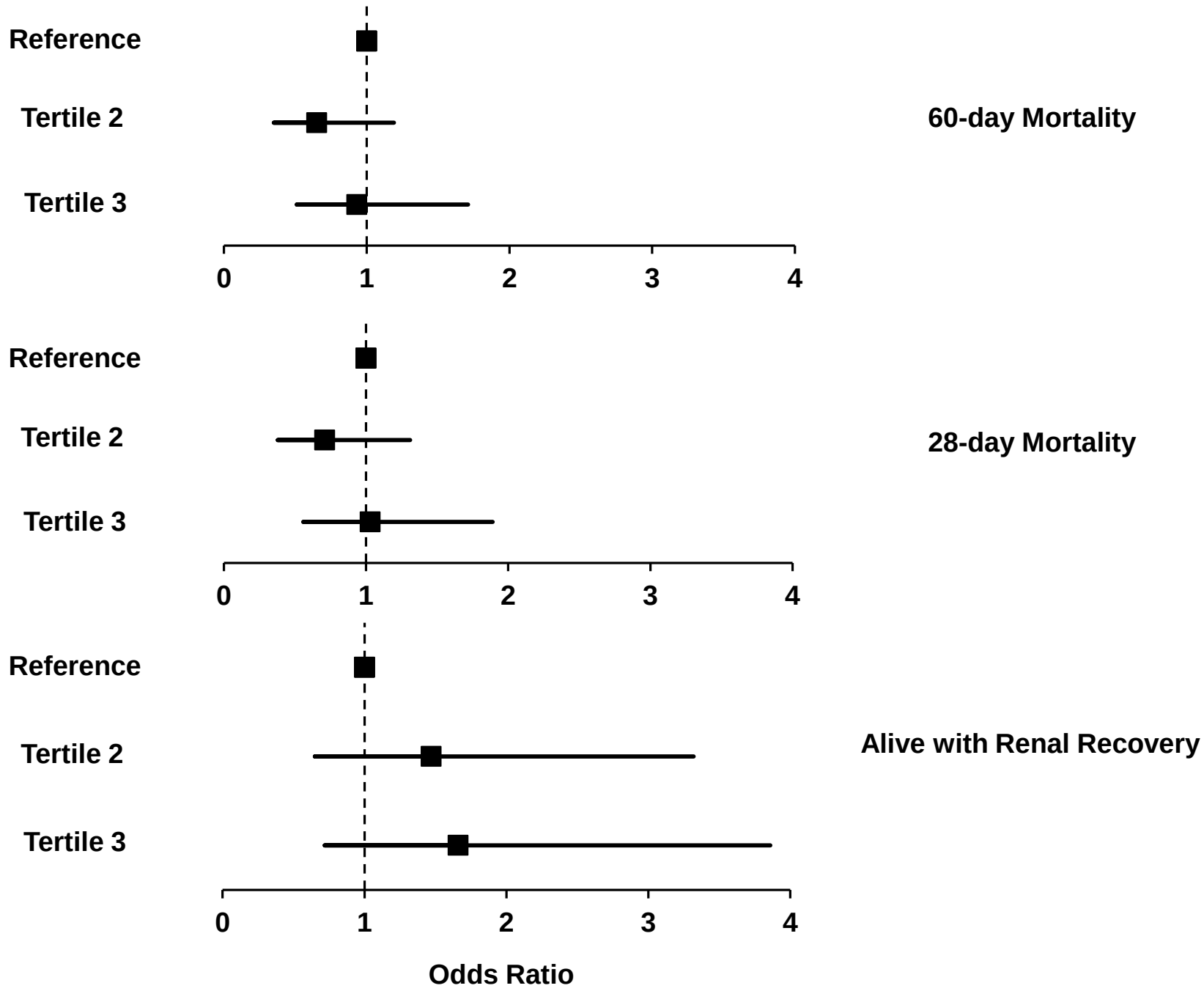


Figure 3



Supplemental Material

Uric Acid and Acute Kidney Injury in the Critically Ill

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Supplemental Tables

- **Table S1**. Baseline Characteristics of the ICU Cohort by AKI Status
- **Table S2**. Baseline Characteristics of ATN Study Participants by 60-day Mortality
- **Table S3~~1~~.** Baseline Characteristics in the ATN Study: Participants not in Subcohort vs Subcohort included in this study.
- **Table S4~~2~~.** Unadjusted Predictors of Uric Acid in the ATN Study Cohort

Table S1. Baseline Characteristics of the ICU Cohort by AKI Status

Characteristic	All patients (n=208)	Incident AKI* (n=40)	No Incident AKI (n=168)
Plasma ~~U~~uric ~~A~~acid, mg/dl	4.7 [3.6 – 6.4]	5.7 [4.1 – 7.8]	4.6 [3.5 – 6.2]
Demographics			
Female, n (%)	94 (45.2)	19 (47.5)	75 (44.6)
Age, years	61.8 ± 15.3	64.4 ± 13.1	61.2 ± 15.7
White, n (%)	177 (85.1)	31 (77.5)	146 (86.9)
Enrollment Characteristics			
SCr, mg/dl	0.8 [0.6 – 1.0]	1.0 [0.8 – 1.2]	0.7 [0.6 – 0.9]
eGFR, ml/min/1.73m^2	91.1 ± 26.6	76.1 ± 28.6	94.7 ± 24.9
APACHE II	17 [12 – 24]	15 [12 – 23]	17 [13 – 25]
Sepsis, n (%)	113 (54.3)	23 (57.5)	90 (53.6)
Etiology, n (%)			
Multifactorial	~~18 (8.7)~~	18 (45.0)	-
Ischemic	~~9 (4.3)~~	9 (22.5)	-
Pre-renal	~~6 (2.9)~~	6 (15.0)	-
Sepsis	~~5 (2.4)~~	5 (12.5)	-
Other	~~2 (1.0)~~	2 (5.0)	-
Co-morbid Conditions, n (%)			
Active malignancy	84 (40.4)	12 (30.0)	72 (42.9)
Chronic lung disease	49 (23.6)	17 (42.5)	32 (19.1)
Diabetes mellitus	44 (21.2)	13 (32.5)	31 (18.5)
Congestive heart failure	12 (5.8)	5 (12.5)	7 (4.2)
Chronic liver disease	10 (4.8)	3 (7.5)	7 (4.2)
ICU type, n (%)			
Medical	112 (53.9)	17 (42.5)	95 (56.5)
Surgical	96 (46.1)	23 (57.5)	73 (43.5)

Data presented as mean ± standard deviation (SD), or median with interquartile range [IQR] for continuous variables and frequencies for binary variables. Estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration equation.

*KDIGO stage 1 AKI or greater

Table S2. Baseline Characteristics of ATN Study Participants by 60-day Mortality

Characteristics	All participants (n=250)	60-day mortality (n=125)	No 60-day mortality (n=125)
Plasma ~~U~~uric ~~A~~acid, mg/dl	11.1 [8.6 – 14.2]	11.1 [8.3 – 14.2]	11.1 [9.0 – 13.8]
Demographics			
Female, n (%)	77 (30.8)	39 (31.2)	38 (30.4)
Age, years	62.0 ± 14.6	64.5 ± 13.1	59.4 ± 15.7
White, n (%)	199 (79.6)	97 (77.6)	102 (81.6)
Pre-morbid Characteristics			
SCr, mg/dl	1.1 [0.8 – 1.4]	1.0 [0.8 – 1.3]	1.1 [0.8 – 1.4]
eGFR, ml/min/1.73m^2	69.1 ± 32.8	70.5 ± 31.8	67.7 ± 34.0
Weight, kg	76.4 ± 15.6	76.4 ± 16.5	76.4 ± 14.7
Co-morbid Conditions*, n (%)			
Cardiovascular disease	82 (32.8)	45 (36.0)	37 (29.6)
Diabetes ~~M~~mellitus	72 (28.8)	40 (32.0)	32 (25.6)
Malignancy	50 (20.0)	24 (19.2)	26 (20.8)
Immunocompromised	35 (14.0)	14 (11.2)	21 (16.8)
Cerebrovascular disease	29 (11.6)	17 (13.6)	12 (9.6)
Chronic ~~H~~hypoxemia	25 (10.0)	16 (12.8)	9 (7.2)
Enrollment Characteristics			
BUN prior to RRT, mg/dl	69.5 ± 30.1	68.9 ± 31.4	70.1 ± 28.8
SCr prior to RRT, mg/dl	4.1 [3.0 – 5.6]	3.6 [2.8 – 5.0]	4.7 [3.6 – 6.0]
Mean Arterial Pressure, mmHg	76.0 ± 15.4	73.6 ± 15.6	78.5 ± 14.8
Urine volume, ml/24 hrs	195 [72 – 545]	124 [52 – 410]	280 [127 – 825]
Urine volume, ml/hr	10.9 [4.2 – 26.0]	6.1 [2.3 – 18.2]	15.3 [6.4 – 40.9]
Oliguria, n (%)	189 (75.6)	102 (81.6)	87 (69.6)
Mechanical Ventilation, n (%)	189 (75.6)	106 (84.8)	83 (66.4)
APACHE II	26 [21 – 31]	28 [24 – 33]	23 [20 – 29]
SOFA Cardiovascular, n (%)			
0-2	102 (40.8)	38 (30.4)	64 (51.2)
3-4	148 (59.2)	87 (69.6)	61 (48.8)
Treatment, n (%)			
Intensive	122 (48.8)	61 (48.8)	61 (48.8)
Less-intensive	128 (51.2)	64 (51.2)	64 (51.2)
ICU type, n (%)			
Medical	122 (48.8)	59 (47.2)	63 (50.4)
Surgical	108 (43.2)	53 (42.4)	55 (44.0)
Other	20 (8.0)	13 (10.4)	7 (5.6)
Post-surgical, n (%)	126 (50.4)	63 (50.4)	63 (50.4)
Etiology of AKI, n (%)			
Ischemic	198 (79.2)	94 (75.2)	104 (83.2)
Nephrotoxic	48 (19.2)	17 (13.6)	31 (24.8)
Sepsis	132 (52.8)	70 (56.0)	62 (49.6)
Multifactorial	135 (54.0)	68 (54.4)	67 (53.6)

Data presented as mean ± SD, or median [IQR] for continuous variables and frequencies for binary or categorical variables. eGFR was determined using the Modification of diet in renal disease (MDRD) equation. *Cardiovascular disease includes participants with a history of myocardial infarction, angina, or congestive heart failure. Diabetes mellitus includes participants with a history of end organ disease from diabetes, use of diabetic diet, or on diabetic medications. Malignancy includes participants with a history of leukemia and tumors with or without metastasis. Immunocompromised includes participants with a history of human immunodeficiency virus, acquired immune deficiency syndrome, or on immunosuppressive therapy. Cerebrovascular disease includes participants with a history of transient ischemic attack or stroke.

Table S3. Baseline Characteristics in the ATN Study: Participants not in Subcohort vs Subcohort included in this study

Characteristics	ATN Study Not in Subcohort (n=874)	ATN Study Subcohort (n=250)	P
Demographics			
Female, %	254 (29.1)	77 (30.8)	0.6
Age, years	59.0 ± 15.4	62.0 ± 14.6	0.006
White, %	635 (72.7)	199 (79.6)	0.03
Pre-morbid Characteristics			
SCr, mg/dl	1.1 [0.9 – 1.4]	1.1 [0.8 – 1.4]	0.9
eGFR, ml/min/1.73m^2	72.1 ± 41.5	69.1 ± 32.8	0.3
Co-morbid Conditions, %			
Cardiovascular disease	327 (37.4)	82 (32.8)	0.2
Diabetes ~~M~~mellitus	251 (28.7)	72 (28.8)	0.9
Malignancy	174 (19.9)	50 (20.0)	0.8
Immunocompromised	143 (16.4)	35 (14.0)	0.4
Cerebrovascular disease	93 (10.6)	29 (11.6)	0.6
Chronic ~~H~~hypoxemia	82 (9.4)	25 (10.0)	0.6
Enrollment Characteristics			
BUN prior to RRT, mg/dl	58.0 ± 30.0	69.5 ± 30.1	<0.001
SCr prior to RRT, mg/dl	3.4 [2.5 – 4.6]	4.1 [3.0 – 5.6]	<0.001
Urine volume, ml/24 hrs	180 [50 – 405]	195 [72 – 545]	0.01
Oliguria, %	686 (78.4)	189 (75.6)	0.3
Mechanical Ventilation, %	715 (81.8)	189 (75.6)	0.02
APACHE II	26 [21 – 32]	26 [21 – 31]	0.8
SOFA Cardiovascular, %			0.1
0-2	407 (46.6)	102 (40.8)	
3-4	467 (53.6)	148 (59.2)	
Treatment, %			0.6
Intensive	441 (50.5)	122 (48.8)	
Less-intensive	433 (49.5)	128 (51.2)	
60-day mortality, %	466 (53.3)	125 (50.0)	0.4

Table S4. Unadjusted Predictors of Uric Acid in the ATN Study Cohort

Variable	Δ Uric Acid, mg/dl	95% CI	P
Age, per year	-0.05	-0.09, -0.007	0.02
Female	-0.54	-1.81, 0.73	0.4
eGFR (pre-morbid) per 1 ml/min	-0.005	-0.02, 0.01	0.6
SCr (pre-morbid) per 1 mg/dl	0.84	-0.88, 2.55	0.3
SCr (enrollment) per 1 mg/dl	0.65	0.35, 0.96	<0.001
Δ SCr per 1 mg/dl	0.60	0.26, 0.94	<0.001
Admit BUN per 1 mg/dl	0.05	0.03, 0.07	<0.001
Recent BUN per 1 mg/dl	0.04	0.02, 0.05	<0.001
Δ BUN per 1 mg/dl	-0.001	-0.02, 0.02	0.9
Race: Non-white vs White	0.12	-1.34, 1.57	0.9
Diabetes mellitus	0.69	-0.63, 2.02	0.3
Natural log urine volume (mL)/24hr	0.004	-0.33, 0.34	0.9
Randomization arm (high vs less intense)	-0.13	-1.30, 1.05	0.8
APACHE II, per 1 point	0.02	-0.07, 0.10	0.7
SOFA (3-4 vs 0-2)	-0.25	-1.45, 0.95	0.7
Mechanical ventilation	-0.07	-1.44, 1.30	0.9

Supplemental Material

Uric Acid and Acute Kidney Injury in the Critically Ill

Anand Srivastava, MD, MPH, Ragnar Palsson, MD, David E. Leaf, MD, MMSc, Angelica Higuera, MD, Polly Palacios, MSPH, Rebecca M. Baron, MD, Venkata Sabbisetti, PhD, Andrew N. Hoofnagle, MD, PhD, Sucheta M. Vaingankar, PhD, Paul M. Palevsky, MD, and Sushrut S. Waikar, MD, MPH

Supplemental Tables

- **Table S1**. Baseline Characteristics of the ICU Cohort by AKI Status
- **Table S2**. Baseline Characteristics of ATN Study Participants by 60-day Mortality
- **Table S3.** Baseline Characteristics in the ATN Study: Participants not in Subcohort vs Subcohort included in this study.
- **Table S4.** Unadjusted Predictors of Uric Acid in the ATN Study Cohort

Table S1. Baseline Characteristics of the ICU Cohort by AKI Status

Characteristic	All patients (n=208)	Incident AKI* (n=40)	No Incident AKI (n=168)
Plasma uric acid, mg/dl	4.7 [3.6 – 6.4]	5.7 [4.1 – 7.8]	4.6 [3.5 – 6.2]
Demographics			
Female, n (%)	94 (45.2)	19 (47.5)	75 (44.6)
Age, years	61.8 ± 15.3	64.4 ± 13.1	61.2 ± 15.7
White, n (%)	177 (85.1)	31 (77.5)	146 (86.9)
Enrollment Characteristics			
SCr, mg/dl	0.8 [0.6 – 1.0]	1.0 [0.8 – 1.2]	0.7 [0.6 – 0.9]
eGFR, ml/min/1.73m^2	91.1 ± 26.6	76.1 ± 28.6	94.7 ± 24.9
APACHE II	17 [12 – 24]	15 [12 – 23]	17 [13 – 25]
Sepsis, n (%)	113 (54.3)	23 (57.5)	90 (53.6)
Etiology, n (%)			
Multifactorial	-	18 (45.0)	-
Ischemic	-	9 (22.5)	-
Pre-renal	-	6 (15.0)	-
Sepsis	-	5 (12.5)	-
Other	-	2 (5.0)	-
Co-morbid Conditions, n (%)			
Active malignancy	84 (40.4)	12 (30.0)	72 (42.9)
Chronic lung disease	49 (23.6)	17 (42.5)	32 (19.1)
Diabetes mellitus	44 (21.2)	13 (32.5)	31 (18.5)
Congestive heart failure	12 (5.8)	5 (12.5)	7 (4.2)
Chronic liver disease	10 (4.8)	3 (7.5)	7 (4.2)
ICU type, n (%)			
Medical	112 (53.9)	17 (42.5)	95 (56.5)
Surgical	96 (46.1)	23 (57.5)	73 (43.5)

Data presented as mean ± standard deviation (SD), or median with interquartile range [IQR] for continuous variables and frequencies for binary variables. Estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration equation.

*KDIGO stage 1 AKI or greater

Table S2. Baseline Characteristics of ATN Study Participants by 60-day Mortality

Characteristics	All participants (n=250)	60-day mortality (n=125)	No 60-day mortality (n=125)
Plasma uric acid, mg/dl	11.1 [8.6 – 14.2]	11.1 [8.3 – 14.2]	11.1 [9.0 – 13.8]
Demographics			
Female, n (%)	77 (30.8)	39 (31.2)	38 (30.4)
Age, years	62.0 ± 14.6	64.5 ± 13.1	59.4 ± 15.7
White, n (%)	199 (79.6)	97 (77.6)	102 (81.6)
Pre-morbid Characteristics			
SCr, mg/dl	1.1 [0.8 – 1.4]	1.0 [0.8 – 1.3]	1.1 [0.8 – 1.4]
eGFR, ml/min/1.73m^2	69.1 ± 32.8	70.5 ± 31.8	67.7 ± 34.0
Weight, kg	76.4 ± 15.6	76.4 ± 16.5	76.4 ± 14.7
Co-morbid Conditions*, n (%)			
Cardiovascular disease	82 (32.8)	45 (36.0)	37 (29.6)
Diabetes mellitus	72 (28.8)	40 (32.0)	32 (25.6)
Malignancy	50 (20.0)	24 (19.2)	26 (20.8)
Immunocompromised	35 (14.0)	14 (11.2)	21 (16.8)
Cerebrovascular disease	29 (11.6)	17 (13.6)	12 (9.6)
Chronic hypoxemia	25 (10.0)	16 (12.8)	9 (7.2)
Enrollment Characteristics			
BUN prior to RRT, mg/dl	69.5 ± 30.1	68.9 ± 31.4	70.1 ± 28.8
SCr prior to RRT, mg/dl	4.1 [3.0 – 5.6]	3.6 [2.8 – 5.0]	4.7 [3.6 – 6.0]
Mean Arterial Pressure, mmHg	76.0 ± 15.4	73.6 ± 15.6	78.5 ± 14.8
Urine volume, ml/24 hrs	195 [72 – 545]	124 [52 – 410]	280 [127 – 825]
Urine volume, ml/hr	10.9 [4.2 – 26.0]	6.1 [2.3 – 18.2]	15.3 [6.4 – 40.9]
Oliguria, n (%)	189 (75.6)	102 (81.6)	87 (69.6)
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SCr (pre-morbid) per 1 mg/dl	0.84	-0.88, 2.55	0.3
SCr (enrollment) per 1 mg/dl	0.65	0.35, 0.96	<0.001
Δ SCr per 1 mg/dl	0.60	0.26, 0.94	<0.001
Admit BUN per 1 mg/dl	0.05	0.03, 0.07	<0.001
Recent BUN per 1 mg/dl	0.04	0.02, 0.05	<0.001
Δ BUN per 1 mg/dl	-0.001	-0.02, 0.02	0.9
Race: Non-white vs White	0.12	-1.34, 1.57	0.9
Diabetes mellitus	0.69	-0.63, 2.02	0.3
Natural log urine volume (mL)/24hr	0.004	-0.33, 0.34	0.9
Randomization arm (high vs less intense)	-0.13	-1.30, 1.05	0.8
APACHE II, per 1 point	0.02	-0.07, 0.10	0.7
SOFA (3-4 vs 0-2)	-0.25	-1.45, 0.95	0.7
Mechanical ventilation	-0.07	-1.44, 1.30	0.9