



Association between urine microscopy and severe acute kidney injury in critically ill patients following non-cardiac surgery: a prospective cohort study

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Background: Acute kidney injury (AKI) is a common and adverse complication following non-cardiac surgery. Evidence have shown urine microscopy could help early detection, differentiating the causes and predicting the progression of AKI. However, little evidence is available on AKI after non-cardiac surgery. Thus, we investigated the association between urine microscopy and severe AKI in critically ill patients after non-cardiac surgery.

Methods: This was a single-center prospective cohort study. The primary outcome was severe AKI, defined as stage 2 or 3 according to maximal KDIGO criteria within 7 days following non-cardiac surgery. Urine microscopy immediately, 6 and 12 hours after surgical intensive care unit (SICU) admission were examined and graded by a urine microscopy score (UMS) based on the observed quantification of renal tubular cells and casts in the sediment. Then, multivariate Logistic regression models were used to analyze the associations between UMS and postoperative severe AKI.

Results: From May 20, 2019 to November 24, 2020, 661 patients were enrolled with 147 patients (22.2%) developing postoperative severe AKI. Multivariate Logistic regression model showed elevated UMS (≥ 1) 6 and 12 hours after SICU admission were independently associated with postoperative severe AKI (OR 2.200, 95% CI: 1.182–4.095, $P=0.013$ and OR 2.949, 95% CI: 1.657–5.248, $P<0.001$, respectively). Furthermore, higher UMS 6 hours after SICU admission demonstrated correlation with greater risk of severe AKI with OR 3.887 (95% CI: 1.430–10.563) for UMS ≥ 3 and OR 2.429 (95% CI: 1.237–4.770) for UMS =1–2. The specificity and sensitivity of UMS ≥ 1 for severe AKI was 93.8% (95% CI: 91.7–95.9%) and 15.6% (95% CI: 9.7–21.5%), respectively. While the negative and positive predictive value was 79.5% (95% CI: 76.3–82.7%) and 41.8% (95% CI: 28.8–54.8%), respectively. In addition, patients with higher UMS (≥ 3 , 1–2 and 0) had significantly more postoperative complications and longer SICU stay; and they also showed a trend toward other adverse postoperative outcomes.

Conclusions: Early urine microscopy was independently associated with severe AKI in critically ill patients following non-cardiac surgery with higher UMS related to greater risk.

Trial Registration: ClinicalTrials.gov identifier: NCT03880110.

Keywords: Acute kidney injury (AKI); urine microscopy; critically ill patients; non-cardiac surgery; early detection

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Introduction

Acute kidney injury (AKI) is an important complication after non-cardiac surgery which has a high incidence (1,2), especially in critically ill surgical patients with rate up to nearly 40% (3). Several underlying susceptibilities, procedures, or exposures have been recognized as risk factors of AKI during the perioperative period (4). More and more evidence has verified the deleterious impact of AKI, especially severe AKI on both short and long term outcomes of surgical patients. Compared to patients with non or mild AKI, patients with severe AKI were associated with increased mortality and higher risk of progressing to chronic kidney disease (CKD) and cardiovascular diseases. Severe AKI patients also had longer length of hospital stay, increased healthcare costs and an increased likelihood of discharge to a health care facility (2,3,5-8). Unfortunately, so far no specific treatment for severe AKI has been established (9), strongly suggesting the necessity of early recognizing patients who will develop severe AKI.

Urine microscopy is an easily accessible and economical test that is widely used for clinical assessment to predict or diagnose kidney disease and monitor the course of disease or response to therapy in those with known kidney disease (10). Accumulated studies have demonstrated the evaluation of urine sediment was especially helpful in early detection of AKI (11,12), differentiating renal AKI from pre-renal AKI (13) and predicting the progression of AKI (14,15). For different patient populations, urine microscopy showed a very high specificity in the diagnosis of AKI in patients from emergency department (12) or undergoing open cardiac surgery (16).

However, limited data focused on critically ill patients following non-cardiac surgery, of which AKI presented a distinct pathophysiology from other types of AKI (4). We hypothesized that critically ill patients with severe AKI after non-cardiac surgery would have different patterns of renal tubular cells and/or casts in the urine sediment and that these would provide additional diagnostic information. Therefore, the purpose of this study was to investigate the association between urine microscopy and severe AKI in critically ill patients after non-cardiac surgery. We present the following article in accordance with the STROBE reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-3085/rc>).

Methods

Ethics and consent

This was a prospective cohort study registered at ClinicalTrials.gov (NCT03880110). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Clinical Research Ethics Committee of Peking University First Hospital on April 10, 2019 (No.: 2019-075) and informed consent was taken from all the patients.

Patients

This study was performed from May 20, 2019 to November 24, 2020 in a teaching hospital affiliated with a university. Patients with at least one of the following conditions would admit to SICU after surgery: (I) preoperative comorbidities, including hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, cerebrovascular disease, CKD and so on; (II) major surgery, defined as surgery duration ≥ 2 h; (III) ongoing organ dysfunction, defined as the sequential organ failure assessment (SOFA) score ≥ 2 from one single organ system. In this study, adult patients undergoing non-cardiac surgery and then immediately admitted to surgical intensive care unit (SICU) were consecutively enrolled. Patients with any of the following criteria were excluded: (I) CKD stage 5 or requiring long-term dialysis; (II) undergoing kidney-related surgery; (III) AKI events before admission to SICU; (IV) without Foley catheter placement; (V) written informed consent not obtained.

Urine microscopy

Fresh urine samples were collected from patients' Foley catheters which were placed at the beginning of anesthesia, and then prepared and examined by specially assigned and experienced investigators within 1 hour. Urine samples were centrifuged (Baiyang, 600C) at 400 g for 5 min to maximize yield and concentrated 50-fold by resuspending the deposit. By using an Olympus BX43 phase contrast

Table 1 Urine microscopy score

Score [renal tubular epithelial cells per HPF]	Score [granular cast per HPF]			
	0 [0]	1 [1]	2 [2–4]	3 [≥5]
0 [0]	0	1	2	3
1 [1]	1	2	3	4
2 [2–4]	2	3	4	5
3 [≥5]	3	4	5	6

HPF, high power field.

microscope, urine sediment was evaluated with $\times 10$, $\times 20$ and $\times 40$ magnification objectives and a $\times 10$ magnification eyepiece. A single drop of urine sediment was placed on S-Y Double Grid Counting Slide 10. After low power fields (LPFs) scanning, high power fields (HPFs) were used to further differentiate epithelial cells, renal tubular epithelial cells (RTEC) and granular casts, which were then counted and averaged.

There is a strict protocol for quality control of urine microscopy, including inter-observer variability. Specifically, the department of clinical laboratory will conduct inter-observer comparison every 6 months. In which, 5 urine sediment samples with at least 3 abnormal are prepared, and then casts and cells are examined and averaged under at least 20 LPFs and 10 HPFs, respectively. Taking the results from specialist in urine microscopy as reference, the following criteria are adopted. When casts are ≤ 10 /LPF or > 10 /LPF, the difference of results should be < 3 /LPF or < 5 /LPF, respectively; when cells are ≤ 10 /HPF, between 10 and 100/HPF or > 100 /HPF, the difference of results should be < 3 /HPF, < 10 /HPF or < 20 /HPF, respectively. Furthermore, the urine microscopy of our clinical laboratory is also qualified by external quality assessment from National Center for Clinical Laboratories twice a year and International Organization for Standardization 15189 reassessment every two years.

Results of urine sediment were graded by urine microscopy score (UMS) outlined in *Table 1* (16) and elevated UMS was defined as ≥ 1 .

Data collection and study outcomes

Patients' data were prospectively collected during their hospital stay by one special researcher. Follow-up visit was performed according to a prespecified protocol from patients' enrollment until their discharge, death or

30 days after surgery, whichever came first. Preoperative data included demographic characteristics, body mass index (BMI), medical history, American Society of Anesthesiology (ASA) physical status classification, nephrotoxin exposure and clinical laboratory data; while intraoperative data contained information of surgery and anesthesia (type, location and duration), estimated blood loss, urine output, and management such as vasopressors infusion, blood products transfusion and fluid balance; for postoperative data, urine microscopy immediately, 6 and 12 hours after SICU admission were collected. Non-renal SOFA score and acute physiology and chronic health evaluation II (APACHE II) score within 24 hours of SICU admission were assessed for the severity of illness.

The primary outcome was severe AKI development, defined as AKI stage 2 or 3, within 7 days after surgery. Postoperative AKI and its severity was defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria using the maximal change in serum creatinine compared with the preoperative baseline values and urine output (17). Serum creatinine was examined at admission to SICU and daily at 6 am within 7 days after surgery, while urine output was closely monitored during the SICU stay.

The secondary outcomes were the postoperative use of mechanical ventilation (MV) and its duration, vasopressors infusion ≥ 24 hours, length of SICU and postoperative hospital stay, number of postoperative complications other than AKI (*Table S1*), and in-hospital mortality.

Relevant data underlying the main results is available at <https://cdn.amegroups.cn/static/public/apm-21-3085-01.xlsx>.

Statistical analysis

Perioperative data were firstly compared among patients without AKI, with mild AKI and with severe AKI, respectively. Then these data were further compared between patients with and without severe AKI. Quantitative variables with normal distribution were compared by independent samples *t*-test or one-way ANOVA; while Mann-Whitney U or Kruskal-Wallis test was used for non-normal distribution. Qualitative variables were compared by Chi-squared test or Fisher's exact test. Time-to-event data were analyzed with Kaplan-Meier survival analysis, with difference between groups compared by Log-rank test. After testing for collinearity, perioperative variables with $P < 0.10$ in the univariate analyses or considered clinically important for severe AKI were included in multivariate logistic regression model (backward LR method) to adjust

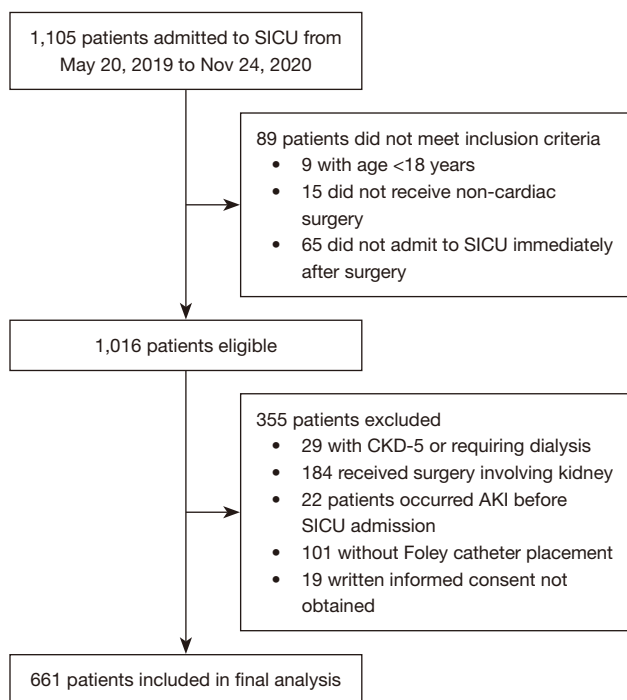


Figure 1 Flow diagram of the study. SICU, surgical intensive care unit; CKD, chronic kidney disease; AKI, acute kidney injury.

the association between UMS and severe AKI. Two-sided P values <0.05 were regarded as statistically significant. The SPSS v21.0 software package was used for statistical processing (SPSS Inc., Chicago, IL, USA).

Results

A total of 1,105 patients were admitted to SICU during the study period. After screening for inclusion and exclusion criteria, 661 patients were finally recruited (Figure 1). Among the enrolled patients, the incidence of severe AKI within 7 days after surgery was 22.2% (147 patients) with AKI stage 2 and 3 accounting for 20.5% (136 patients) and 1.7% (11 patients), respectively. The median time to AKI and severe AKI diagnosis after SICU admission was 9.3 (6.0, 16.2) and 14.3 (12.0, 21.6) hours. The actual median sampling time for immediately, 6 and 12 hours of urine microscopy was 0.8 (0.0, 0.3), 6.0 (6.0, 6.1) and 12.0 (12.0, 12.1) hours after SICU admission, respectively. Baseline and perioperative data were listed in Table 2 and Table 3. For preoperative variables, age, BMI, history of CKD, hemoglobin and albumin, baseline serum creatinine and estimated glomerular filtration rate (eGFR), use

of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and smoking habit showed significant difference among groups, while for intra and postoperative variables, intraoperative urine output, postoperative elevated UMS 6 and 12 hours after admission, non-renal SOFA score and APACHE II score after 24 hours of SICU admission were statistically different.

In contrast to patients without AKI and with mild AKI (Tables S2,S3), patients with severe AKI had higher age and BMI, lower baseline eGFR and decreased level of preoperative hemoglobin and albumin. More patients with severe AKI used ACEI or ARB preoperatively. In addition, less intraoperative urine output and fluid balance were seen in severe AKI patients, who also had higher non-renal SOFA score and APACHE II score.

Furthermore, as shown in Table S3, more patients with severe AKI had elevated UMS immediately, 6 and 12 hours after SICU admission than patients without severe AKI (12.9% vs. 7.2%, $P=0.028$; 15.6% vs. 6.2%, $P<0.001$; 19.7% vs. 6.3%, $P<0.001$, respectively). In multivariate logistic regression model, elevated UMS 6 and 12 hours after SICU admission were independently associated with postoperative severe AKI (OR 2.200, 95% CI: 1.182–4.095, $P=0.013$ and OR 2.949, 95% CI: 1.657–5.248, $P<0.001$, respectively) after adjusting for age, BMI, history of coronary heart disease and CKD, ASA classification, preoperative hemoglobin and albumin, baseline eGFR, use of ACEI or ARB, intraoperative urine output and fluid balance and non-renal SOFA score after 24 hours of SICU admission (Table 4). In addition, as shown in Figure 2, UMS began to elevate 8 hours earlier than the diagnosis of severe AKI.

Moreover, taking UMS 0 as reference, higher UMS 6 hours after SICU admission demonstrated well correlation with greater risk of severe AKI with OR 3.887 (95% CI: 1.430–10.563) for UMS ≥ 3 and OR 2.429 (95% CI: 1.237–4.770) for UMS =1–2. These relationships remained even after adjusting for the above factors with OR 3.097 (95% CI: 1.050–9.139) for UMS ≥ 3 and OR 1.952 (95% CI: 0.942–4.044) for UMS =1–2 (Figure 3). The specificity of UMS ≥ 3 and ≥ 1 for severe AKI were 98.4% (95% CI: 97.3–99.5%) and 93.8% (95% CI: 91.7–95.9%), while the sensitivity were 5.4% (95% CI: 1.7–9.1%) and 15.6% (95% CI: 9.7–21.5%), respectively. The positive predictive values of UMS ≥ 3 and ≥ 1 for severe AKI were 50.0% (95% CI: 25.5–74.5%) and 41.8% (95% CI: 28.8–54.8%), and the negative predictive values were 78.4% (95% CI: 75.2–81.6%) and 79.5% (95% CI: 76.3–82.7%), respectively.

To improve the usefulness of UMS in clinical situation,

Table 2 Preoperative variables

	Total (n=661)	Without AKI (n=361)	With mild AKI (n=153)	With severe AKI (n=147)	P value
Age (y)	69±15	66±15	71±14	73±14	<0.001
Male sex	402 (60.8%)	229 (63.4%)	81 (52.9%)	92 (62.6%)	0.074
BMI (kg/m ²)	24.0±4.0	23.5±3.8	24.3±4.2	24.9±4.3	0.001
Preoperative comorbidities					
Diabetes mellitus	187 (28.3%)	102 (28.3%)	40 (26.1%)	45 (30.6%)	0.691
Hypertension	403 (61.0%)	207 (57.3%)	207 (64.7%)	97 (66.0%)	0.108
Coronary heart disease	223 (33.7%)	114 (31.6%)	51 (33.3%)	58 (39.5%)	0.233
Congestive heart failure	86 (13.0%)	39 (10.8%)	24 (15.7%)	23 (15.6%)	0.180
Cerebrovascular disease	122 (18.5%)	59 (16.3%)	30 (19.6%)	33 (22.4%)	0.251
Chronic kidney disease	76 (11.5%)	29 (8.0%)	25 (16.3%)	22 (15.0%)	0.009
ASA classification					0.114
I-II	113 (17.1%)	71 (19.7%)	24 (15.7%)	18 (12.2%)	
III-IV	548 (82.9%)	290 (80.3%)	129 (84.3%)	129 (87.8%)	
Preoperative Hb (g/L) ^a	124±22	126±21	122±22	121±22	0.014
Preoperative albumin (g/L) ^a	38.8±5.2	39.6±5.1	38.2±5.5	37.4±5.0	<0.001
Baseline serum Cr (μmol/L) ^b	81.1±31.0	77.8±24.8	86.1±41.0	84.0±31.8	0.009
Baseline eGFR (mL/min/1.73 m ²) ^c	80.2±21.7	83.9±20.3	75.7±22.5	76.0±22.5	<0.001
Radiocontrast exposure ^d	56 (8.5%)	32 (8.9%)	11 (7.2%)	13 (8.8%)	0.810
On ACEI/ARB	104 (15.7%)	42 (11.6%)	31 (20.3%)	31 (21.1%)	0.006
Smoking habit ^e	213 (32.2%)	130 (36.0%)	31 (20.3%)	52 (35.4%)	0.001

Data are presented as mean ± SD or number of patients (percentage) and compared by one-way ANOVA, Kruskal-Wallis test or chi-squared test/Fisher's exact test respectively. ^a, measured within 3 days before surgery. ^b, determined by the minimal value of serum creatinine measured within 3 months before admission and in hospital before surgery; if neither value was available, the modification of diet in renal disease formula was adopted to estimate the baseline serum creatinine according to the Kidney Disease Improving Global Outcomes guideline. ^c, estimated by the modification of diet in renal disease formula. ^d, including patients who had radiocontrast exposure within 2 days before surgery. ^e, smoking for more than 10 cigarettes per day for more than 1 year, including current or past smokers. AKI, acute kidney injury; BMI, body mass index; ASA, American society of anesthesiologists; Hb, hemoglobin; Cr, creatinine; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ANOVA, analysis of variance.

we further analyzed risk factors related to the development of postoperative severe AKI (Table S4) and the results showed that age (y) [OR 1.026 (95% CI: 1.010–1.042)], BMI (kg/m²) [OR 1.082 (95% CI: 1.028–1.140)], preoperative albumin (g/L) [OR 0.956 (95% CI: 0.919–0.994)] and intraoperative urine output (mL/kg/h) [OR 0.818 (95% CI: 0.688–0.972)] were independently associated with severe AKI.

In addition, patients with higher UMS (≥3, 1–2 and 0) after 6 hours of admission had significantly more postoperative complications [1 (0, 2), 0 (0, 1) and 0 (0, 0), P=0.018] (Table 5, Table S1) and longer SICU stay [3.0 (1.1,

4.9), 2.0 (1.3, 2.7) and 1.0 (0.9, 1.1), P=0.015]; and they also showed a trend toward other adverse postoperative outcomes, such as longer duration of MV and vasopressors infusion; more days of postoperative hospital stay and increased in-hospital mortality (Table 5).

Discussion

Results of this prospective study demonstrated that urine microscopy 6 hours after SICU admission was independently associated with severe AKI occurrence in

Table 3 Intra- and post-operative variables

	Total (n=661)	Without AKI (n=361)	With mild AKI (n=153)	With severe AKI (n=147)	P value
Duration of anesthesia (min)	292±141	293±135	297±156	282±140	0.642
Duration of surgery (min)	212±134	214±128	214±149	206±134	0.824
Emergency surgery	39 (5.9%)	20 (5.5%)	11 (7.2%)	8 (5.4%)	0.742
Open surgery ^a	243 (46.2%)	118 (42.1%)	63 (51.6%)	62 (50.0%)	0.134
Type of surgery					0.193
Abdominal and pelvic surgery	447 (67.6%)	240 (66.5%)	99 (64.7%)	108 (73.5%)	
Thoracic surgery	67 (10.1%)	34 (9.4%)	20 (13.1%)	13 (8.8%)	
Neurosurgery	33 (5.0%)	25 (6.9%)	5 (3.3%)	3 (2.0%)	
Orthopedic surgery	98 (14.8%)	52 (14.4%)	27 (17.6%)	19 (12.9%)	
Others ^b	16 (2.4%)	10 (2.8%)	2 (1.3%)	4 (2.7%)	
Estimated blood loss (mL)	100 [50, 300]	100 [50, 300]	100 [50, 400]	100 [50, 300]	0.746
Urine output (mL/kg/h)	1.5 (0.9, 2.6)	1.7 (1.0, 2.9)	1.4 (0.8, 2.1)	1.2 (0.7, 1.9)	<0.001
Intraoperative management					
Vasopressors infusio ^c	334 (50.5%)	181 (50.1%)	75 (49.0%)	78 (53.1%)	0.764
Blood products transfusion ^d	146 (22.1%)	77 (21.3%)	43 (28.1%)	26 (17.7%)	0.082
Fluid balance (mL/kg/h)	6.5±4.2	6.8±4.7	6.6±3.8	5.8±3.0	0.058
Postoperative variables					
Elevated UMS at admission ^e	56 (8.5%)	24 (6.6%)	13 (8.5%)	19 (12.9%)	0.070
Elevated UMS 6 hours after admission ^e	55 (8.3%)	20 (5.5%)	12 (7.8%)	23 (15.6%)	0.001
Elevated UMS 12 hours after admission ^e	61 (9.3%)	14 (3.9%)	18 (11.8%)	29 (19.7%)	<0.001
Non-renal SOFA score ^f	3 (2, 4)	2 (2, 4)	3 (2, 4)	3 (2, 5)	<0.001
APACHE II score ^f	12±4	12±4	12±4	13±5	<0.001
D0 Fluid balance (mL/kg)	32.0 (19.8, 46.5)	29.9 (17.4, 43.3)	34.3 (21.5, 49.7)	33.5 (22.7, 48.9)	0.012
D0 Urine output (mL/kg)	20.4 (12.7, 31.7)	25.7 (15.9, 36.6)	18.8 (12.1, 26.6)	12.6 (8.3, 18.4)	<0.001

Data are presented as mean ± SD, median (interquartile range), or number of patients (percentage) and compared by one-way ANOVA, Kruskal-Wallis test or chi-squared test/Fisher's exact test respectively. ^a, open or laparoscopic surgery referred to 526 patients. ^b, including peripheral vascular surgery, ear, nose and throat surgery and thyroid or breast surgery. ^c, including use of phenylephrine, norepinephrine, epinephrine, and dopamine. ^d, including packed red blood cell, plasma, and platelet. ^e, defined as UMS ≥1. ^f, calculated after 24 hours of SICU admission. AKI, acute kidney injury; UMS, urine microscopy score; SOFA, sequential organ failure assessment score; APACHE, acute physiology and chronic health evaluation; D0, the day of surgery; ANOVA, analysis of variance; SICU, surgical intensive care unit.

critically ill patients following non-cardiac surgery with higher UMS related to greater risk. Elevated UMS had a high specificity and negative predictive value, but a relatively low sensitivity and positive predictive value for severe AKI detection. Furthermore, patients with increased UMS tended to have worse outcomes. Considering the lack of data on the relationship between urine microscopy and

AKI after non-cardiac surgery, our study provided valuable information and strengthened evidence on this field.

In our study, the incidence of severe AKI (defined as AKI stage ≥2) after surgery was 22.2%, while in the study conducted by Park and colleagues (18), the incidence of critical AKI (defined as AKI stage ≥2 and AKI that consequently led to post-AKI death or dialysis) was 1.1%

Table 4 Association between elevated urine sediment score and postoperative severe AKI

	Univariate logistic model		Multivariate logistic model ^a	
	OR (95% CI)	P value	OR (95% CI)	P value
Elevated UMS at admission	1.914 (1.064–3.440)	0.030	–	–
Elevated UMS 6 hours after admission	2.794 (1.578–4.945)	<0.001	2.200 (1.182–4.095)	0.013
Elevated UMS 12 hours after admission	3.686 (2.145–6.335)	<0.001	2.949 (1.657–5.248)	<0.001

^a, factors with P values <0.10 in univariate analyses or considered clinically important were included in the multivariate logistic regression model with backward LR method for adjustment. These included age, body mass index, history of coronary heart disease and chronic kidney disease, ASA classification, preoperative hemoglobin and albumin, baseline eGFR, use of ACEI or ARB, intraoperative urine output and fluid balance and non-renal SOFA score after 24 hours of SICU admission. CI, confidence interval; OR, odds ratio; UMS, urine microscopy score; ASA, American Society of Anesthesiologists; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

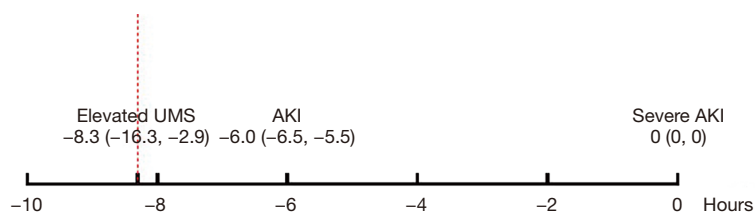


Figure 2 Time axis for elevated UMS, AKI and severe AKI. This figure showed the time relation between firstly elevated UMS and the diagnosis of AKI and severe AKI. Taking the diagnostic time point of severe AKI as reference, data are presented as median (interquartile range). UMS, urine microscopy score; AKI, acute kidney injury.

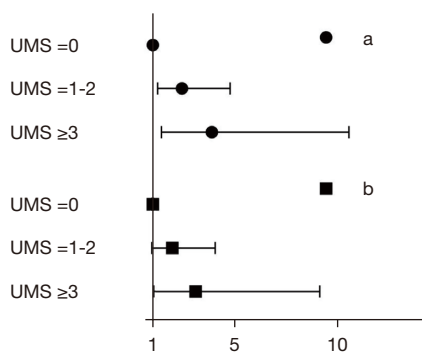


Figure 3 Association between UMS and severe AKI. This figure showed the association between UMS 6 hours after SICU admission and severe AKI. The black circle or square and corresponding outline indicated odds ratio and 95% confidence interval. a: Univariate logistic regression model of severe AKI with UMS 0 as reference. b: Multivariate logistic regression model of severe AKI with UMS 0 as reference, adjusting for age, body mass index, history of coronary heart disease and chronic kidney disease, ASA classification, preoperative hemoglobin and albumin, baseline eGFR, use of ACEI or ARB, intraoperative urine output and fluid balance and non-renal SOFA score after 24 hours of ICU admission. UMS, urine microscopy score; AKI, acute kidney injury; SICU, surgical intensive care unit; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SOFA, sequential organ failure assessment.

Table 5 UMS and postoperative outcomes

	UMS ^a =0 (n=606)	UMS ^a =1–2 (n=39)	UMS ^a ≥3 (n=16)	P value
MV	301 (49.7%)	24 (61.5%)	10 (62.5%)	0.225
Duration of MV (h) ^b	6.0 (5.3, 6.8)	9.0 (5.4, 12.6)	10.0 (0.0, 22.4)	0.354
Vasopressors infusion ≥24 hours ^c	44 (7.3%)	5 (12.8%)	3 (18.8%)	0.120
Number of postoperative complications ^d	0 (0, 0)	0 (0, 1)	1 (0, 2)	0.018
Length of SICU stay (d) ^e	1.0 (0.9, 1.1)	2.0 (1.3, 2.7)	3.0 (1.1, 4.9)	0.015
Postoperative hospital stay (d) ^e	9.0 (8.5, 9.5)	11.0 (8.4, 13.6)	12.0 (7.3, 16.7)	0.257
In-hospital mortality	10 (1.7%)	0 (0.0%)	1 (6.3%)	0.257

Data are presented as number of patients (percentage) or median (interquartile range), unless otherwise indicated. ^a, urine microscopy scores 6 hours after SICU admission. ^b, results of patients requiring postoperative mechanical ventilation. Data were analyzed by Kaplan-Meier analysis and compared by Log-rank test; results are presented as median (95% confidence interval). ^c, including use of phenylephrine, norepinephrine, epinephrine, and dopamine. ^d, including pulmonary infection, pleural effusion, atelectasis, respiratory failure, acute myocardial infarction, new-onset arrhythmia, hemodynamic insufficiency, stroke, venous thromboembolism, ileus, intra-abdominal abscess, wound infection, urinary tract infection, sepsis, surgical bleeding, digestive tract bleeding, acute liver injury, disseminated intravascular coagulation, anastomotic leakage, and wound dehiscence (Table S1). ^e, data were analyzed by Kaplan-Meier analysis and compared by Log-rank test; results are presented as median (95% confidence interval). UMS, urine microscopy score; MV, mechanical ventilation; SICU, surgical intensive care unit.

in the discovery cohort and 1.5% in the validation cohort, respectively. We thought there were two possible reasons. Firstly, compared to Park's study which included patients in general ward, our study mainly focused on critically ill patients following non-cardiac surgery who had more complex and severe perioperative conditions. Secondly, in our study, postoperative AKI and its severity was defined according to both serum creatinine and urine output criteria, while Park's study only used serum creatinine criteria which might underestimate the incidence of severe AKI.

Several studies have been undertaken to elucidate the relationship between urine microscopy and early detection of AKI. In 1979, the research of Schentag *et al.* (11), demonstrated that urinary casts were significantly higher in nephrotoxic AKI, defined as increase in serum creatinine ≥0.5 mg/dL within 5 days after aminoglycoside treatment, and increased as early as 9 days before changes of serum creatinine in patients from intensive care unit. Schinstock and colleagues (12) conducted a study focused on emergency patients and found that the overall agreement of presence of any RTECs or RTEC/granular casts and severe AKI was 85.4% (95% CI: 81.4–88.7%). In a study on patients following open cardiac surgery, urine sediment were significantly higher in AKI patients and appeared as early as just 2 hours after termination of cardiopulmonary bypass (CPB) (19). Our data showed a higher rate of elevated UMS in severe AKI patients even just immediately

after surgery and the independent association of UMS 6 hours after SICU admission with severe AKI. UMS elevated as early as 8 hours before diagnosis of severe AKI. All of which would reinforce the previous findings and suggested that early elevated UMS in critically ill patients after non-cardiac surgery was independently associated with severe AKI. Furthermore, higher UMS was related to greater risk.

In accordance with the study on emergency patients (12), in which abnormal urine microscopy had a specificity of 89.9% (95% CI: 86.2–92.7%) and sensitivity of 29.6% (95% CI: 15.9–48.5%) for severe AKI, our results showed the specificity and sensitivity for severe AKI were 93.8% (95% CI: 91.7–95.9%) and 15.6% (95% CI: 9.7–21.5%), respectively. However, urine microscopy 12 hours after CPB was found to be highly sensitive and specific for cardiac surgery related AKI with area under the curve of 0.888 (95% CI: 0.746–1.029) (19). The possible explanation might be that patients undergoing cardiac surgery, especially with CPB, were exposed to a number of risk factors and then several mechanisms, such as ischemia-reperfusion injury, inflammation, oxidative stress, hemolysis and nephrotoxins, combined together to result in more severe renal tubular injury (20) which likely had positive manifestations of RTECs or RTEC/granular casts in urine sediment.

Urine output was a key diagnostic criterion of AKI, but its reliability in perioperative patients was getting controversial because there was a physiologic reduction

in urine output as a result from hypovolemia, anesthesia and release of aldosterone and vasopressin in response to stress (21). In addition, elevations in serum creatinine might also not always represent renal injury which was commonly contributed to hemodynamic reduction in renal blood flow during perioperative period (22). As shown in *Table 3*, patients with severe AKI had significantly reduced intraoperative and D0 (the day of surgery) urine output. Furthermore, although severe AKI patients had more positive D0 fluid balance, there was a trend that they received less fluid balance during surgery. Therefore, pre-renal factor might partly contribute to the development of severe AKI. Differentiating structural AKI from those functional AKI was rather important for risk stratification and subsequent management in patients undergoing non-cardiac surgery. Searching for cell types and casts by urine microscopy examination was very helpful in differential diagnosis of the AKI causes. A purely pre-renal AKI often resulted in urinary sediment that was bland or characterized by hyaline casts, while the presence of RTECs or RTEC/granular casts usually indicated tubular structural injury (10).

In addition, due to higher UMS suggesting more severe renal tubular injury, urine microscopy could also be utilized as a test of predicting short-term prognosis. In our study, patients with early elevated UMS had significantly more postoperative complications and longer SICU stay; and they also showed a trend toward other adverse postoperative outcomes. Several studies have also demonstrated that, in patients with AKI, UMS was positively associated with increase in AKI stage, renal replacement therapy, renal non-recovery and even death during hospitalization (14–16,23).

Our study demonstrated that elevated UMS 6 and 12 hours after SICU admission was independently associated with postoperative severe AKI. Considering the limited time window for renal protection, we thought the time point for measuring UMS might be 6 hours after surgery. Elevated UMS showed a high specificity (93.8%) and negative predictive value (79.5%), while its sensitivity (15.6%) and positive predictive value (41.8%) were low. On one hand, urine microscopy early after non-cardiac surgery could be used as a measurement assisting severe AKI exclusion in patients with risk factors, such as higher age and BMI, preoperative hypoalbuminemia and intraoperative oliguria (*Table S4*). On the other hand, urine microscopy could be combined with other more sensitive novel injury biomarkers to improve early AKI detection, such as neutrophil gelatinase-associated lipocalin and kidney injury

molecule-1 (12,19,24). Furthermore, as an easily accessible and economical examination, urine microscopy might play a more important role in resource limited regions. To sum up, the observations in our study would further assert the complementary value of inclusion of urine microscopy in early risk stratification and diagnosis of severe AKI in critically ill patients following non-cardiac surgery.

There were some limitations in our study. Firstly, postoperative urine output was closely monitored during SICU stay but not when patients transferred back to general ward within 7 days after surgery which might underestimate the incidence and severity of AKI. However, the majority of AKI occurred during the early days of ICU admission (25), thus the possible underestimation was minimized. Secondly, previous study on patients after open cardiac surgery (19) showed UMS began to increase just 2 hours after CPB and nearly achieved peak 12 hours after CPB in AKI patients. Therefore, in this study postoperative urine microscopy was examined immediately, 6 and 12 hours after SICU admission. However, the optimal time point of urine microscopy to independently predict the association with severe AKI still need to be explored. Because of the limited time window leaving for postoperative AKI prevention, our study still provided useful information for future study design. Finally, as a single center study, the generalizability of our results might be limited.

Conclusions

Early urine microscopy was independently associated with severe AKI in critically ill patients following non-cardiac surgery with higher UMS related to greater risk. Urine microscopy was suggested in early risk stratification and diagnosis of severe AKI.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Clinical Research Ethics Committee of Peking University First Hospital on April 10, 2019 (No.: 2019-075) and informed consent was taken from all the patients.

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Table S1 Occurrence of other postoperative complications. Demonstrates the occurrence and definitions of other postoperative complications

Complications	UMS ^a =0 (n=606)	UMS ^a =1-2 (n=39)	UMS ^a ≥3 (n=16)	P value
Pulmonary complications				
Pulmonary infection ^b	41 (6.8%)	4 (10.3%)	3 (18.8%)	0.144
Pleural effusion ^c	6 (1.0%)	1 (2.6%)	1 (6.3%)	0.120
Atelectasis ^d	24 (4.0%)	1 (2.6%)	0 (0.0%)	0.657
Respiratory failure ^e	19 (3.1%)	2 (5.1%)	2 (12.5%)	0.110
Surgical bleeding ^f	14 (2.3%)	0 (0.0%)	0 (0.0%)	0.523
New onset arrhythmia ^g	20 (3.3%)	4 (10.3%)	0 (0.0%)	0.058
Acute myocardial infarction ^h	10 (1.7%)	0 (0.0%)	0 (0.0%)	0.631
Hemodynamic insufficiency ⁱ	44 (7.3%)	5 (12.8%)	3 (18.8%)	0.120
Stroke ^j	10 (1.7%)	0 (0.0%)	1 (6.3%)	0.257
Ileus ^k	14 (2.3%)	1 (2.6%)	1 (6.3%)	0.598
Anastomotic leakage ^l	24 (4.0%)	1 (2.6%)	1 (6.3%)	0.810
Intra-abdominal abscess ^m	6 (1.0%)	2 (5.1%)	0 (0.0%)	0.066
Acute liver injury ⁿ	10 (1.7%)	0 (0.0%)	0 (0.0%)	0.631
Wound infection ^o	12 (2.0%)	0 (0.0%)	0 (0.0%)	0.574
Wound dehiscence ^p	7 (1.2%)	1 (2.6%)	0 (0.0%)	0.667
Urinary tract infection ^q	7 (1.2%)	0 (0.0%)	0 (0.0%)	0.725
Sepsis ^r	33 (5.4%)	1 (2.6%)	4 (25.0%)	0.003
Disseminated intravascular coagulation ^s	7 (1.2%)	0 (0.0%)	0 (0.0%)	0.725
Digestive tract bleeding ^t	14 (2.3%)	1 (2.6%)	0 (0.0%)	0.822
Venous thromboembolism				
Pulmonary embolism ^u	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Deep venous thrombosis ^v	19 (3.1%)	0 (0.0%)	1 (6.3%)	0.405

Data are presented as number of patients (percentage) and compared by chi-squared test. ^a, Urine microscopy score after 6 hours of admission. ^b, Presence of at least one of the following manifestations (increased or color-changed sputum, new or changed pulmonary infiltrates, fever, leukocyte count >12,000/mm³) and required antibiotic therapy. ^c, Confirmed by chest X-ray or ultrasound examination and required therapeutic intervention (drainage, aspiration, and/or diuresis after albumin administration). ^d, Confirmed by chest X-ray examination, with or without oxygen desaturation, and required therapeutic intervention (oxygenation inhalation, physical therapy, and/or mechanical ventilation). ^e, Presence of the following manifestations (PaO₂ <60 mmHg on room air, ratio of PaO₂ to inspired oxygen fraction <300 mmHg, or oxygen saturation <90%) and required therapeutic intervention (oxygen therapy or mechanical ventilation) for more than 24 hours. ^f, Bleeding after surgery that required secondary surgical hemostasis. ^g, New onset atrial fibrillation or paroxysmal supraventricular tachycardia that necessitated medical treatment. ^h, Concentration of cardiac troponin I exceed the diagnostic criteria for myocardial infarction as well as new Q waves (lasts for 0.03 s) or continuous (4 days) abnormal ST-T segment. ⁱ, Requirement of continuous infusion of inotropic agents or vasoconstrictors to maintain MAP≥65mmHg after surgery. ^j, Persisted new focal neurologic deficit and confirmed by neurologic imaging. ^k, Lack of bowel movement, flatulence, and requirement of parenteral nutrition for more than 1 week after surgery. ^l, Extravasation of contrast agent in the body cavity or retroperitoneal space that required percutaneous drainage. ^m, Clinical manifestations combined with evidence from B ultrasound or CT scan. ⁿ, Elevation of serum transaminase level above 3 times the upper limit, excluded myocardial and skeletal muscle injury. ^o, Pus expressed from the incision, and bacteria cultured from the pus. ^p, Wound rupture that required secondary suturing. ^q, Confirmed by urinalysis and urine culture and necessitated antibiotic therapy. ^r, Defined as infection with acute change of SOFA score≥2, according to sepsis 3.0 diagnostic criteria. ^s, Symptoms of bleeding combined with prolonged prothrombin time and activated partial thromboplastin time, decreased fibrinogen and increased level of D-Dimer and fibrinogen degradation product. ^t, Decrease of hemoglobin level combined with positive gastrointestinal occult blood test results that required treatment. ^u, Pulmonary embolism: confirmed by CTPA. ^v, Deep venous thrombosis: confirmed by deep venous ultrasonography.

Table S2 Preoperative variables. Demonstrates preoperative variables between patients with or without severe AKI

	Total (n=661)	Without severe AKI (n=514) ^a	With severe AKI (n=147)	P value
Age (y)	69±15	68±15	73±14	<0.001
Male sex	402 (60.8%)	310 (60.3%)	92 (62.6%)	0.618
BMI (kg/m ²)	24.0±4.0	23.7±3.9	24.9±4.3	0.002
Preoperative comorbidities				
Diabetes mellitus	187 (28.3%)	142 (27.6%)	45 (30.6%)	0.478
Hypertension	403 (61.0%)	306 (59.5%)	97 (66.0%)	0.157
Coronary heart disease	223 (33.7%)	165 (32.1%)	58 (39.5%)	0.096
Congestive heart failure	86 (13.0%)	63 (12.3%)	23 (15.6%)	0.281
Cerebrovascular disease	122 (18.5%)	89 (17.3%)	33 (22.4%)	0.157
Chronic kidney disease	76 (11.5%)	54 (10.5%)	22 (15.0%)	0.135
ASA classification				0.076
I-II	113 (17.1%)	95 (18.5%)	18 (12.2%)	
III-IV	548 (82.9%)	419 (81.5%)	129 (87.8%)	
Preoperative Hb (g/L) ^b	124±22	125±21	121±22	0.041
Preoperative albumin (g/L) ^b	38.8±5.2	39.2±5.2	37.4±5.0	<0.001
Baseline serum Cr (umol/L) ^c	81.1±31.0	80.3±30.7	84.0±31.8	0.192
Baseline eGFR (mL/min/1.73 m ²) ^d	80.2±21.7	81.4±21.3	76.0±22.5	0.007
Radiocontrast exposure ^e	56 (8.5%)	43 (8.4%)	13 (8.8%)	0.854
On ACEI/ARB	104 (15.7%)	73 (14.2%)	31 (21.1%)	0.043
Smoking habit ^f	213 (32.2%)	161 (31.3%)	52 (35.4%)	0.354

Data are presented as mean ±SD, or number of patients (percentage) and compared by independent samples *t*-test, Mann-Whitney U test or chi-squared test/Fisher's exact test respectively. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, American society of anesthesiologists; BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin. ^a, Including patients without AKI and with mild AKI. ^b, Measured within 3 days before surgery. ^c, Determined by the minimal value of serum creatinine measured within 3 months before admission and in hospital before surgery; if neither value was available, the modification of diet in renal disease formula was adopted to estimate the baseline serum creatinine according to the Kidney Disease Improving Global Outcomes guideline. ^d, Estimated by the modification of diet in renal disease formula. ^e, Including patients who had radiocontrast exposure within 2 days before surgery. ^f, Smoking for more than 10 cigarettes per day for more than 1 year, including current or past smokers.

Table S3 Intra- and postoperative variables. Demonstrates intra- and postoperative variables between patients with or without severe AKI

	Total (n=661)	Without severe AKI (n=514) ^a	With severe AKI (n=147)	P value
Duration of anesthesia (min)	292±141	294±142	282±140	0.372
Duration of surgery (min)	212±134	214±135	206±134	0.534
Emergency surgery	39 (5.9%)	31 (6.0%)	8 (5.4%)	0.789
Open surgery ^b	243 (46.2%)	181 (45.0%)	62 (50.0%)	0.331
Type of surgery				0.278
Abdominal and pelvic surgery	447 (67.6%)	339 (66.0%)	108 (73.5%)	
Thoracic surgery	67 (10.1%)	54 (10.5%)	13 (8.8%)	
Neurosurgery	33 (5.0%)	30 (5.8%)	3 (2.0%)	
Orthopedic surgery	98 (14.8%)	79 (15.4%)	19 (12.9%)	
Others ^c	16 (2.4%)	12 (2.3%)	4 (2.7%)	
Estimated blood loss (mL)	100 (50, 300)	100 (50, 300)	100 (50, 300)	0.503
Urine output (mL/kg/h)	1.5 (0.9, 2.6)	1.7 (0.9, 2.7)	1.2 (0.7, 1.9)	<0.001
Intraoperative management				
Vasopressors infusion ^d	334 (50.5%)	256 (49.8%)	78 (53.1%)	0.486
Blood products transfusion ^e	146 (22.1%)	140 (23.3%)	26 (17.7%)	0.145
Fluid balance (mL/kg.h)	6.5±4.2	6.7±4.4	5.8±3.0	0.005
Postoperative variables				
Elevated UMS at admission ^f	56 (8.5%)	37 (7.2%)	19 (12.9%)	0.028
Elevated UMS 6 hours after admission ^f	55 (8.3%)	32 (6.2%)	23 (15.6%)	<0.001
Elevated UMS 12 hours after admission ^f	61 (9.3%)	32 (6.3%)	29 (19.7%)	<0.001
Non-renal SOFA score ^g	3 (2, 4)	3 (2, 4)	3 (2, 5)	0.003
APACHE II score ^g	12±4	12±4	13±5	<0.001
D0 Fluid balance (mL/kg)	32.0 (19.8, 46.5)	31.1 (18.6, 45.9)	33.5 (22.7, 48.9)	0.058
D0 Urine output (mL/kg)	20.4 (12.7, 31.7)	23.7 (14.3, 34.0)	12.6 (8.3, 18.4)	<0.001

Data are presented as mean ±SD, median (interquartile range), or number of patients (percentage) and compared by independent samples *t*-test, Mann-Whitney U test or chi-squared test/Fisher's exact test respectively. ^a, Including patients without AKI and with mild AKI. ^b, Open or laparoscopic surgery referred to 526 patients. ^c, Including peripheral vascular surgery, ear, nose and throat surgery and thyroid or breast surgery. ^d, Including use of phenylephrine, norepinephrine, epinephrine, and dopamine. ^e, Including packed red blood cell, plasma, and platelet. ^f, Defined as UMS ≥1. ^g, Calculated after 24 hours of SICU admission. APACHE, acute physiology and chronic health evaluation; D0, the day of surgery; SOFA, sequential organ failure assessment score; UMS, urine microscopy score.

Table S4 Pre-and intra-operative risk factors of postoperative severe AKI. Demonstrates uni-and multi-variate Logistic model of severe AKI

	Univariate Logistic model		Multivariate Logistic model ^a	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (y)	1.029 (1.014–1.044)	<0.001	1.026 (1.010–1.042)	0.002
BMI (kg/m ²)	1.073 (1.026–1.122)	0.002	1.082 (1.028–1.140)	0.003
History of coronary heart disease	1.378 (0.944–2.014)	0.097	–	–
ASA classification (III–IV vs. I–II)	1.625 (0.946–2.791)	0.079	–	–
Preoperative Hb (g/L) ^b	0.991 (0.983–1.000)	0.042	–	–
Preoperative albumin (g/L) ^b	0.939 (0.907–0.972)	<0.001	0.956 (0.919–0.994)	0.023
Baseline eGFR (mL/min/1.73 m ²) ^c	0.989 (0.980–0.997)	0.008	–	–
On ACEI/ARB	1.614 (1.012–2.576)	0.045	–	–
Intraoperative urine output (mL/kg.h)	0.732 (0.620–0.865)	<0.001	0.818 (0.688–0.972)	0.023
Intraoperative fluid balance (mL/kg.h)	0.941 (0.894–0.991)	0.021	–	–

^a, After excluding variables of collinearity, factors with P values < 0.10 in univariate analyses or considered clinically important were included in the multivariate logistic regression model with backward LR method for adjustment. ^b, Measured within 3 days before surgery. ^c, Estimated by the modification of diet in renal disease formula. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, American society of anesthesiologists; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; OR, odds ratio.