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see commentary on page 699

Oliguria is an early predictor of higher mortality in critically ill patients

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Oliguria is a valuable marker of kidney function and a criterion for diagnosing and staging acute kidney injury (AKI). However, the utility of urine output as a specific metric for renal dysfunction is somewhat controversial. To study this issue further we tested whether urine output is a sensitive, specific, and early measure for diagnosing and staging AKI in 317 critically ill patients in a prospective observational study. Urine output was assessed every hour and serum creatinine every 12 to 24 h. The sensitivity and specificity of different definitions of oliguria for the diagnosis of AKI were compared with the Acute Kidney Injury Network serum creatinine criterion. The incidence of AKI increased from 24%, based solely on serum creatinine, to 52% by adding the urine output as a diagnostic criterion. Oliguric patients without a change in serum creatinine had an intensive care unit mortality rate (8.8%) significantly higher than patients without AKI (1.3%), and similar to oliguric patients with an increase in serum creatinine (10.4%). The diagnosis of AKI occurred earlier in oliguric than in non-oliguric patients. Oliguria of more than 12 h and oliguria of 3 or more episodes were associated with an increased mortality rate. Thus, urine output is a sensitive and early marker for AKI and is associated with adverse outcomes in intensive care unit patients.

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KEYWORDS: acute kidney injury; creatinine; critically ill; mortality; oliguria; urine output

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Acute kidney injury (AKI) is associated with a 40–80% mortality rate, increased length of hospital stay, and high costs in critically ill patients.[1–4] Even minor changes in renal function, such as a serum creatinine (sCr) increase of 0.3 mg/dl, are associated with short-term and long-term mortality and the development of chronic kidney disease.[5] It is still unclear whether these changes are a marker for AKI severity or direct mediators of the adverse outcomes. Regardless, the emerging role of declining renal function as a risk factor for mortality advocates an urgent need for early recognition and management of AKI. These data have catalyzed the search for novel, more sensitive, and specific biomarkers to detect AKI earlier. Several candidates are undergoing prospective validation: neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, liver fatty acid-binding protein, α- and π-glutathione *S*-transferase.[6–9]

Although oliguria is a frequent event in intensive care unit (ICU) patients and urine flow has been proposed as a diagnostic and staging criterion for AKI, none of the biomarker studies have focused on urine output (UO) as a renal biomarker. Most of the previous studies were derived from analysis of retrospective data, and the UO criterion, if not omitted, was modified, confirming that its application is challenging and that further studies are required to validate this criterion.

We believe that urine flow rate is a sensitive and specific biomarker that provides an early warning signal for impending renal dysfunction. We hypothesized that the UO criteria would increase the sensitivity and specificity of the Acute Kidney Injury Network (AKIN) classification system, as oliguric patients without sCr change would have an increased mortality, dialysis requirements, and longer lengths of ICU stay than non-AKI patients. In addition, we hypothesized that changes in urine volume would be an earlier marker of AKI in comparison with the sCr criterion. We assessed different definitions of oliguria to determine whether the current standard for AKI diagnosis and staging is optimal in comparison with alternate criteria.

RESULTS

Incidence of oliguria

This study included 317 patients. We assessed the incidence of oliguria using different definitions as presented in Figure 1.

One hundred and fifty one patients (47%) had an episode of oliguria during their ICU stay. More patients were classified as oliguric using the total urine volume over a 6-h period (olig6-moving blocks (mblock) and olig6-fixed blocks (fblock)) compared with the current AKIN UO definition, which requires 6 consecutive hours with <0.5 ml/kg (olig6 consecutive (consec)). Patients who met olig6-consec definition had the highest rate of progression to AKIN stage 2 based on UO criterion, 74/94 (79%). Of these 74, 15 (20%) progressed to olig24 (UO <7.2 ml/kg in 24 h or anuria for 12 h). Olig6-mblock was the most sensitive definition, but had the lowest rate of progression: 70/150 (52%) to stage 2 and 15 (19%) to olig24. The rate of progression of patients who had met olig6-fblock was 64% to olig12 and 19% to olig24.

Table 1 shows the sensitivity, specificity, and positive and negative predictive values of the different oliguria definitions based on AKIN sCr criterion as the gold standard for AKI diagnosis. Olig6-mblock had the highest sensitivity (0.54) and olig6-consec the highest specificity (0.71). Increasing the time frame to detect oliguria from 6 to 12 h (olig12) and to 24 h (olig24) increased the specificity, but markedly decreased the sensitivity compared with the AKIN sCr definition. Within any 6-h interval, olig6-fblock had the best positive and negative predictive values. We used olig6-fblock (i.e., <3 ml/kg during a 6-h fblock) to further classify the patients into four groups: non-AKI, non-oliguric AKI, oliguric with sCr change (Type A), and oliguric without sCr change (Type B).

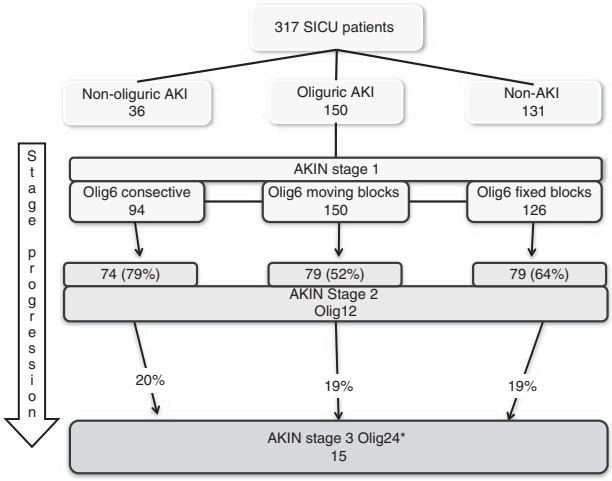

Figure 1 | Patient classification as AKI by AKIN classification system and the proposed oliguria definitions. Definitions: Olig6 con (AKIN stage 1 urine output criterion): <0.5 ml/kg/h for at least 6 consecutive hours. Olig6-mblock (modified criterion): <3 ml/kg during any 6-h period (e.g., 0600–1200 or 0700–1300 hours). Olig6-fblock (modified criterion): <3 ml/kg during a 6-h fblock (e.g., 0600–1200 hours). Olig12 <6 ml/kg during a 12-h block. Olig24 <7.2 ml/kg in 24 h or anuria ⩾12 h. AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; fblock, fixed block; mblock, moving block; Olig, oliguria; SICU, surgical intensive care unit. * indicates outliers.

Of 150 oliguric patients, 64 (42%) had prolonged oliguria (12 h), and 15 (10%) had anuria for 12 h or oliguria for 24 h (AKIN UO Stage 3). We evaluated the distribution of co-morbidities and potentially modifiable acute risk factors for AKI in patients with olig6 and in patients with prolonged oliguria (olig12 and olig24). Patients with prolonged oliguria had more associated co-morbidities and higher incidence of acute risk factors (Table 2). Length of ICU and hospital stay was not different among patients classified by maximum AKIN stage by UO criterion. Need for dialysis and mortality rate was significantly higher in patients classified as stage 3 by UO criterion (Figure 2).

AKI staging progression

At AKI diagnosis of the 167 patients, 56 were non-oliguric (sCr changes alone) and 111 were oliguric (olig6-fblock definition; Figure 3). One hundred and sixty five patients were classified as AKIN stage 1 and two patients were classified as AKIN stage 2 (by the sCr criteria). Fifteen non-oliguric patients had an episode of oliguria after AKI diagnosis and were classified as Type A group (sCr and oliguria by olig6-fblock), based on maximum stage during ICU stay. Of the oliguric patients, 21 subsequently had sCr changes and were also classified as Type A (sCr and oliguria by olig6-fblock). Based on maximum AKIN stage reached, 41 patients were non-oliguric, 36 had oliguric AKI with sCr elevation (Type A) and 90 were oliguric without change in sCr (Type B). Fifteen patients progressed to AKIN stage 2 exclusively by sCr criterion, 8 by both sCr and oliguria criteria, and 71 exclusively by oliguria criteria. A total of 22 patients reached

Table 1 | Sensitivity, specificity, positive, and negative predictive values for UO criteria based on serum creatinine as the standard diagnostic criteria[a]

	AKIN Stage 1			Stage 2	Stage 3
	Olig6-consec[b]	Olig6-mblock	Olig6-fblock	Olig12	Olig24[c]
No. of patients	94	150	126	79	15
Sensitivity	0.34 (0.24–0.45)	0.53 (0.41–0.64)	0.47 (0.35–0.58)	0.30 (0.20–0.41)	0.08 (0.03–0.17)
Specificity	0.71 (0.65–0.77)	0.54 (0.48–0.61)	0.62 (0.56–0.68)	0.76 (0.70–0.81)	0.96 (0.92–0.98)
Positive predictive value	0.27	0.27	0.28	0.29	0.37
Negative predictive value	0.77	0.78	0.79	0.77	0.76

Abbreviations: AKIN, Acute Kidney Injury Network; consec, consecutive; fblock, fixed block; mblock, moving block; Olig, oliguria; UO, urine output.
[a]AKIN stage 1 serum creatinine criterion: absolute 0.3 mg/dl or relative 50% increase from reference serum creatinine within 48 h.
[b]AKIN stage 1 urine output criterion.
[c]Urine output <7.2 ml/kg in 24 h or anuria for 12 h.

Stage 3 criteria; 7 exclusively by sCr, 1 by both criteria, and 14 exclusively by oliguria criteria (Figure 3).

Table 3 compares the demographic and patient characteristics at ICU admission of non-AKI patients, non-oliguric patients, and Type A and B oliguric patients. There was no difference in the number of patients with chronic kidney disease or the reference sCr level among groups. However, Type A oliguric patients were older and had more co-morbidities, with a higher incidence of diabetes mellitus, hypertension, and obesity. Type A oliguric patients also had higher incidence of sepsis and hypotension, required mechanical ventilation and were exposed to nephrotoxic drugs more often.

Table 2 | Risk factors in patients diagnosed as oliguric AKI using a moving block method (*n*=150)

Number of patients	AKIN Stage 1 olig6-mblock	AKIN Stage 2 olig12	AKIN Stage 3 olig24	*P*-value
n (% total)	71 (47)	64 (43)	15 (10)	
Demographic characteristics				
Age years, median (IQR)	52 (35–71)	59 (48–73)	61 (49–70)	0.19
Race—Caucasian	33 (46)	41 (64)	9 (60)	0.27
Gender, male	40 (56)	42 (65)	9 (60)	0.54
BMI (kg/m^2), median (IQR)	27 (23–31)	28 (24–35)	31 (22–38)	0.32
Co-morbidities				
Age >70 years	18 (25)	19 (30)	3 (20)	0.70
Diabetes	14 (20)	24 (37)	9 (60)	0.003
Hypertension	21 (30)	26 (40)	5 (33)	0.40
Obesity (BMI>30)	21 (30)	24 (37)	8 (53)	0.19
Chronic liver disease	8 (11)	9 (14)	7 (43.8)	0.003
Chronic lung disease	10 (14)	4 (6)	7 (46)	<0.001
Congestive heart failure	5 (7)	8 (12)	6 (40)	0.002
Reference sCr (mg/dl), median (IQR)	0.9 (0.7–1.1)	0.9 (0.8–1.3)	1.0 (0.7–1.4)	0.42
Atherosclerotic disease	8 (11)	11 (17)	7 (46)	0.004
Acute risk factors				
Severe infection/sepsis	11 (15)	9 (14)	7 (46)	0.009
Hypotension	23 (32)	18 (28)	12 (80)	0.001
Mechanical ventilation	31 (43)	34 (53)	12 (80)	0.03
pH value ⩽7.30	6 (8)	13 (20)	6 (40)	0.007
Nephrotoxin exposure	10 (14)	11 (17)	6 (40)	0.06

Abbreviations: AKIN, Acute Kidney Injury Network; BMI, body mass index; IQR, interquartile range; mblock, moving block; olig, oliguria; sCr, serum creatinine.

Time to reach diagnostic criteria

We calculated the time to reach AKI diagnosis from ICU admission by oliguria and by sCr criteria. Type B oliguric patients were diagnosed earlier than non-oliguric AKI (UO 12 h (interquartile ratio (IQR) 6–24) vs. sCr 24 h (IQR 12–37); $P=0.008$; Figure 4). In patients who met both criteria (Type A), there was no significant difference in time to reach UO or sCr diagnosis; UO 12 h (IQR 6–27) vs. sCr 14 h (IQR 7–23); $P=0.36$.

Outcomes by AKI diagnostic criteria

The frequency to require renal replacement therapy was different among the groups of AKI diagnosis, but not significantly different between Type A (2.2%) and Type B (13.9%; $P=0.20$) oliguric patients. The lengths of ICU and hospital stay were shorter in non-AKI than in Type B oliguric patients. The ICU length of stay was 2 (IQR 2–3) in non-AKI versus 3 (IQR 2–7) in Type B ($P<0.001$). Hospital length of stay was 6 (IQR 3–13) in non-AKI versus 8 (IQR 4–17) in Type B ($P=0.02$). The overall mortality rate was 5.6% and varied in each group (Figure 5). The mortality rate in AKI patients was 9.5%, compared with 1.3% in non-AKI patients ($P=0.001$). Type B oliguric patients had a significantly higher mortality rate than non-AKI patients (non-AKI 1.3 vs. 8.8% olig6-fblock; $P=0.007$). Applying the UO criterion in addition to the sCr criterion, increases the area under the curve to predict mortality for AKI from 0.60 (95% confidence interval 0.46–0.75; $P=0.12$) to 0.69 (95% confidence interval 0.58–0.79; $P=0.006$).

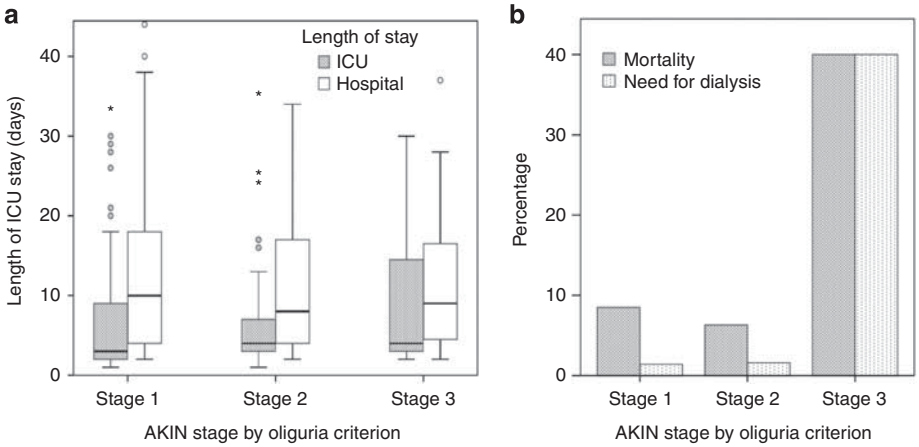

Figure 2 | Outcome in oliguric patients. (**a**) Box plot representing length of ICU and hospital stay and (**b**) bars showing the need for RRT and ICU mortality by AKIN staging based on urine output criteria. *P*-value for difference among the groups: 0.32 for length of ICU stay; 0.98 for length of hospital stay; <0.001 for need for RRT and ICU mortality. *P*-value for difference between stages 1 and 3: 0.005 for need for dialysis and <0.001 for mortality. *P*-value for difference between stages 2 and 3: 0.002 for need for dialysis and <0.001 for mortality. AKIN, Acute Kidney Injury Network; ICU, intensive care unit; RRT, renal replacement therapy. ° and * indicate outliers.

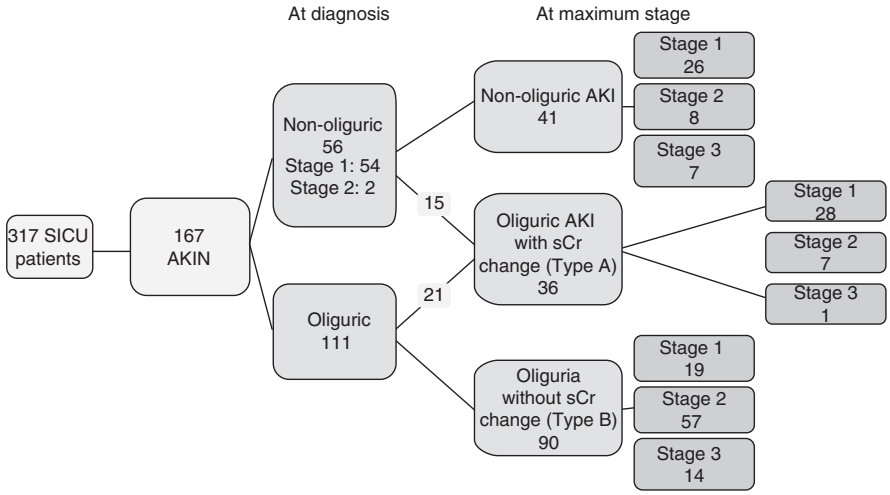

Figure 3 | AKIN classification at diagnosis and maximum stage by sCr and urine output criteria. At AKI diagnosis 56 were non-oliguric (sCr changes alone) and 111 were oliguric (olig6-fblock definition). Fifteen non-oliguric patients had an episode of oliguria after AKI diagnosis and of the oliguric patients, 21 subsequently had sCr changes and were classified as Type A (sCr and oliguria by olig6-fblock). On the basis of the maximum AKIN stage reached, 41 patients were non-oliguric, 36 had oliguric AKI with sCr change (Type A), and 90 were oliguric without change in sCr (Type B). Fifteen patients progressed to AKIN stage 2 exclusively by sCr criterion, 8 by both sCr and oliguria criteria, and 71 exclusively by oliguria criteria. A total of 22 patients reached Stage 3 criteria; 7 exclusively by sCr, 1 by both criteria, and 14 exclusively by oliguria criteria. AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; fblock, fixed block; sCr, serum creatinine; SICU, surgical intensive care unit'.

Table 3 | Patient characteristics by AKI diagnostic criteria

Number of patients, *n* (% total)	Non-AKI 151 (47)	Non-oliguric AKI 41 (13)	Oliguric with sCr change (Type A) 36 (12)	Oliguric without sCr change (Type B) 90 (28)	*P*-value
Demographic characteristics					
Age (years), median (IQR)	42 (27–61)	45 (31–58)	54 (43–76)	59 (48–73)	<0.0001
Race—Caucasian, *n* (%)	71 (47.0)	21 (51.2)	18 (50.0)	53 (58.2)	0.262
Gender, male	95 (62.9)	26 (63.4)	24 (66.7)	55 (60.4)	0.568
BMI (kg/m^2), median (IQR)	25 (22–29)	24 (22–27)	28 (24–35)	27 (24–34)	<0.0001
Reference sCr (mg/dl), median (IQR)	0.8 (0.7–1.0)	1 (0.8–1.2)	1 (0.8–1.3)	0.9 (0.7–1.1)	0.058
Co-morbidities—n (%)					
Age >70 years	19 (12.6)	5 (12.2)	10 (27.8)	25 (27.5)	0.009
Diabetes mellitus	19 (12.6)	5 (12.2)	17 (47.2)	29 (31.9)	<0.0001
Hypertension	27 (17.9)	9 (22.0)	19 (52.8)	25 (27.5)	<0.0001
Morbid obesity	33 (21.9)	4 (9.8)	14 (38.9)	32 (35.2)	0.003
Chronic liver disease	5 (3.3)	7 (17.1)	11 (30.6)	11 (12.1)	<0.0001
Congestive heart failure	3 (2.0)	2 (4.9)	11 (30.6)	7 (7.7)	<0.0001
Chronic lung disease	7 (4.6)	7 (17.1)	10 (27.8)	9 (9.9)	<0.0001
Cerebrovascular accident	28 (18.5)	9 (22.0)	8 (22.2)	22 (24.2)	0.76
Chronic kidney disease	5 (3.3)	2 (4.9)	1 (2.8)	1 (1.1)	0.69
Acute risk factors—n (%)					
Severe infection/sepsis	9 (6.0)	6 (14.6)	15 (41.7)	10 (11.0)	<0.0001
Hypotension	26 (17.2)	11 (26.8)	17 (47.2)	30 (33.0)	0.001
Mechanical ventilation	57 (37.7)	19 (46.3)	25 (69.4)	43 (47.3)	0.007
pH value ⩽7.30	13 (8.6)	5 (12.2)	12 (33.3)	11 (12.1)	0.001
Nephrotoxin exposure	17 (11.3)	9 (22.0)	11 (30.6)	11 (12.1)	0.014

Abbreviations: AKI, acute kidney injury; BMI, body mass index; IQR, interquartile range; sCr, serum creatinine.
Continuous variables are expressed as median (IQR) and categorical variables as frequency (*n*) and percentage (%). *P*-value for the difference among groups.

We evaluated the association of AKI diagnosis and mortality by adjusting for age, cumulative fluid balance (from ICU admission to the day of AKI diagnosis by UO or sCr), sepsis, and need for mechanical ventilation. Table 4 shows that the association of AKI diagnosis with mortality was maintained in non-oliguric, and Type A and B oliguric patients after multivariate adjustment.

Hours of oliguria and number of episodes of oliguria in survivors and non-survivors

The median number of non-consecutive hours with urine volume <0.5 ml/kg was 10 h (IQR 3–22); 22 h (IQR 12–40) for patients with at least one episode of oliguria versus 4 h (IQR 2–7) in patients with no episode of oliguria. Non-survivors had a statistically significant higher non-consecutive

number of hours with urine volume <0.5 ml/kg: 24.5 h (IQR 11.2–37) than survivors: 9 h (IQR 3–21); $P = 0.002$. There was an increment in mortality rate in patients presenting more than 12 h of oliguria (Figure 6). Among patients presenting with oliguria (olig6-fblock), the median number of episodes was 2 (IQR 1–5). Patients with more than three episodes of oliguria presented a significant higher mortality rate than patients with less than three episodes of oliguria (30 vs. 6%; $P = 0.01$; Figure 6).

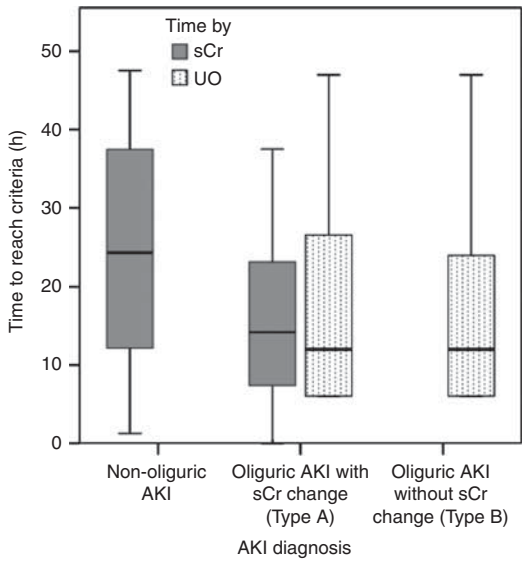

Figure 4 | Time to reach sCr and UO criteria in non-oliguric, Type A, and Type B oliguric patients. Time to reach diagnosis from ICU admission: in solid gray by serum creatinine; in pattern by oliguria criteria. Non-oliguric patients reached sCr after 24 h (IQR 12–37 h). For Type A patients, the time to reach oliguria was 12 h (IQR 6–27 h) and sCr criterion 14 h (IQR 7–23 h), not significantly different: $P = 0.36$. In Type B patients, time to reach oliguria was 12 h (IQR 6–24 h). The difference in time to reach diagnosis between non-oliguric and Type B groups was significant: $P = 0.008$. AKI, acute kidney injury; IQR, interquartile range; sCr, serum creatinine; UO, urine output.

DISCUSSION

Oliguria is a frequent event in ICU patients, being the final pathway for several injuries to renal parenchyma; still oliguria is also the result of transitory changes in volume status or of external influences, such as drug administration. Although the UO is currently included as a criterion to diagnose and stage AKI, few studies have evaluated if decreased UO without elevation in sCr is a specific marker of AKI that correlates with outcomes. A major barrier to the application of the UO criterion is that accurate hourly UO measurements have been difficult to obtain. Urine flow measurements are time-consuming, as urine meters require manipulation, visual assessment, and manual data recording. In most ICUs, nurses empty the collection bag every 6 h. These difficulties in measuring, monitoring, and accurately recording UO have resulted in a lack of a standardized approach to assessing changes in UO and identifying of episodes of oliguria.

While oliguria can be considered a marker of renal function and a criterion that correlates with outcomes, devices providing a continuous and accurate measurement of urine flow are not

Table 4 | Independent predictors for ICU mortality

	OR	95% CI	*P*-value
Non-oliguric AKI			
Sepsis	9.83	4.17–23.12	0.000
AKI diagnosis	2.96	1.21–7.19	0.017
Type B—oliguric AKI without sCr change (definition olig6-mblock)			
AKI diagnosis	5.09	1.69–15.3	0.004
Sepsis	10.91	5.29–22.5	0.000
Type A—oliguric AKI with sCr change			
Age	1.01	1.00–1.02	0.041
Sepsis	6.36	2.44–16.5	0.000
AKI diagnosis	5.56	1.22–25.4	0.027

Abbreviations: AKI, acute kidney injury; CI, confidence interval; ICU, intensive care unit; mblock, moving block; OR, odds ratio; sCr, serum creatinine.
Multivariate analysis adjusting the association of AKI diagnosis (non-oliguric, oliguric with sCr change, and oliguric without sCr change) and mortality for age, cumulative fluid balance (from ICU admission to the day of AKI diagnosis by urine output or sCr), sepsis diagnosis, and need for mechanical ventilation.

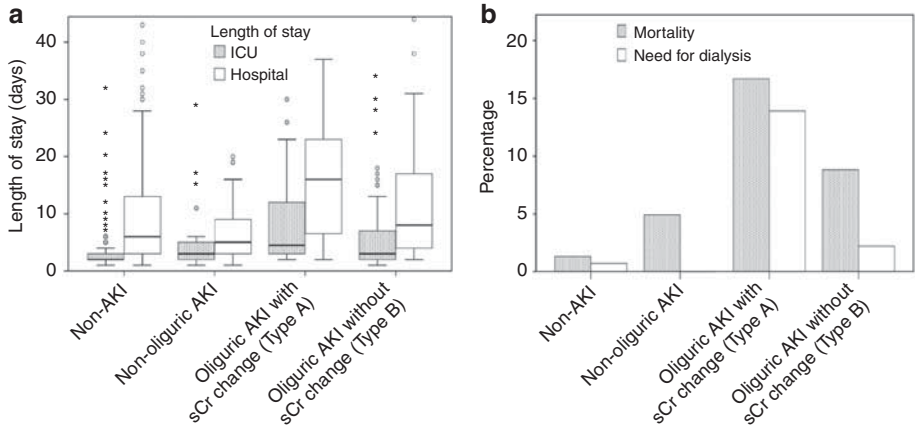

Figure 5 | Clinical outcomes by AKI diagnosis criteria. (**a**) Box plot representing length of ICU and hospital stay by AKI diagnostic criteria. (**b**) Bars show the need for RRT and ICU mortality. *P*-value = 0.002 among the groups for need for RRT and ICU mortality. Type B (AKI oliguric without sCr change) versus non-AKI patients: $P = 0.007$ for ICU mortality; $P = 0.02$ for ICU stay (days); and $P < 0.001$ for hospital stay (days). AKI, acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy; sCr, serum creatinine. ° and * indicate outliers.

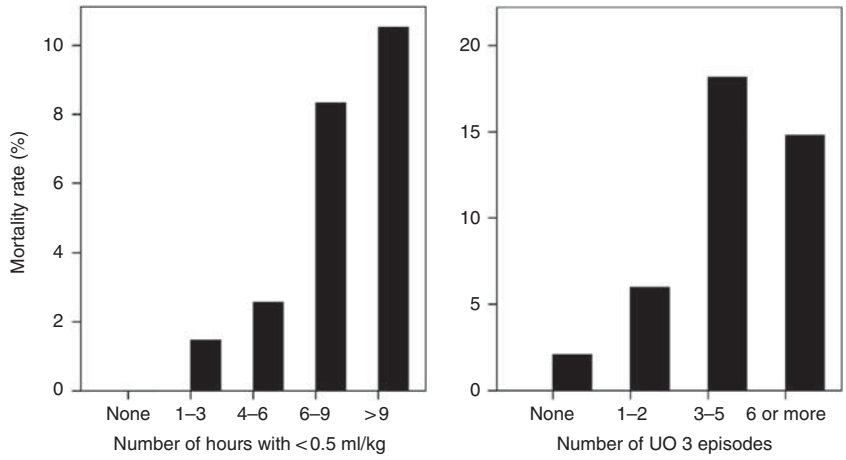

Figure 6 | Mortality rate in patients classified by the duration and number of episodes of oliguria during ICU stay. The mortality rate progressively increases with more non-consecutive hours of oliguria and number of episodes of olig6-fblock (consecutive 6 h with <3 ml/kg). fblock, fixed block; ICU, intensive care unit; UO, urine output.

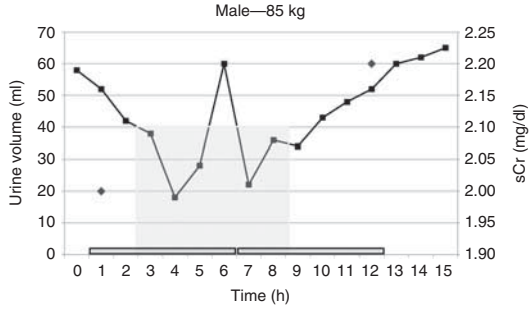

Figure 7 | Urine volume and serum creatinine of a patient classified by the olig6-mblock definition, but not classified by definitions olig6-consecutive and olig6-fblock. A 85 kg patient would be classified as AKI by the olig6-mblock definition (urine volume <3 ml/kg in 6 consecutive hours (light gray rectangle)), however would not be classified by olig6 con (<0.5 ml/kg every hour for 6 consecutive hours) as there was 1 h with an urine volume higher than 0.5 ml/kg/h. Similarly, the olig6-fblock definition was not met as the urine volume was higher than 3 ml/kg in the predefined olig6-fblock 6-h interval (dark rectangles). AKI, acute kidney injury; fblock, fixed block; mblock, moving block; olig, oliguria; sCr, serum creatinine; ■, urine flow; ◆, serum creatinine.

widely available. The hourly information on urine volume, with more frequent observations of the parameter, could allow an earlier detection of renal dysfunction. Treating urine flow as a continuous physiological variable instead of as interval parameter, would provide more time points for the detection of AKI. For intervention trials on prevention and treatment of AKI, accurate hourly monitoring of urine flow would provide more opportunities for intervention.[10] On the other hand, for retrospective evaluations and prospective epidemiological studies, the assessment of total urine volume in a longer time intervals could facilitate the application of the criteria, as most hospitals do not have digital monitors to record UO hourly. Balancing the practicality of using longer time intervals against ascertaining urine flow every hour to diagnose oliguria is challenging. In our study, we initially compared different definitions of oliguria to detect changes in UO. As hourly UO was recorded in the electronic medical record, we developed the olig6-consec calculation to correspond to the strictest interpretation of the UO AKIN criterion, requiring the urine volume to be <0.5 ml/kg every hour during 6 consecutive hours. The olig6-mblock definition was less strict in accepting a cumulative decrease in UO to <3 ml/kg over 6 consecutive hours (Figure 7). However, both these calculations required computation of urine volume in consecutive 6-h periods, requiring a moving reference point to define the 6-h period. This moving reference point adds some complexity to the calculations, and patients may not be classified as AKI if the decline in UO varies over a 6-h interval, as shown in Figure 7. We therefore tested the olig6-fblock and olig12 calculations to evaluate if applying the criterion in blocks of 6 or 12 h, matching a nurse's shift, would facilitate the application without decreasing the sensitivity and specificity of the criterion. We demonstrated that assessing the urine volume in a 6-h interval (olig6-mblock and olig6-fblock) resulted in an increased sensitivity as compared with olig6-consec. Although the assessment of the total urine volume over 6 h decreased the specificity of the criterion, the olig6-fblock definition had the best positive predictive value for AKI, based on sCr criterion (Table 1). We also assessed the stage progression based on UO criterion, and confirmed that patients classified by olig6-consec, the strictest definition, had a higher rate of stage progression, and those classified by olig6-mblock and olig6-fblock had an intermediate rate of progression: 79, 52, and 64%, respectively. As the olig6-fblock definition had the best overall performance, we used that for the subsequent analysis.

Our study confirmed the finding of previous studies that applying the UO criterion in addition to the sCr criterion increases the number of patients diagnosed as AKI. Although the UO increases the sensitivity of the diagnostic criteria, the specificity of this criterion has not been defined.[11–15] In our study, the incidence of AKI increased from 24 to 52% (using sCr criterion only) applying both criteria. Joannidis *et al.*,[11] using SAPS 3 database with more than 16,000 ICU patients, assessed urine volume in a 24-h interval. In that study, they

modified the AKIN UO criterion, classifying patients with <0.5 ml/kg/h in 24 h as injury by the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification. AKI patients classified in the first 48 h of ICU by the worst modified UO criterion had increased mortality in comparison with non-AKI patients. Although oliguric patients had a higher mortality rate than non-AKI patients, the effect of adding the UO criterion to sCr to predict mortality has shown discordant results. Haase *et al.*[12] analyzed patients' outcome classified by UO independently of sCr criteria. Applying UO criterion in the first 48 h had a lower predictive value for in-hospital mortality compared with the sCr criterion. In a systematic review of studies that used both creatinine and UO criteria,[2] the relative risk for death criteria was lower than in those using only the creatinine criterion. However, these studies used modified UO criterion or applied it in a shorter period of time, first 24 or 48 h. In a study by Cruz *et al.*,[14] applying the actual RIFLE criteria during ICU stay, the use of creatinine and UO criteria together had the strongest predictor of ICU mortality in multivariable analysis. In our study, patients exclusively diagnosed by UO criterion had more frequent need for dialysis, longer length of ICU stay, and higher mortality rate than patients without AKI. However, we did not record the reasons for dialysis initiation and cannot attribute the increased dialysis requirement to a specific factor, e.g., fluid balance. Additionally, we demonstrated that applying the UO criteria, in addition to the sCr, increases the ability of the AKIN classification to predict mortality; the area under the receiver operating characteristic curve increased from 0.60 when applying only the sCr criterion to 0.69, including UO and sCr.

An important finding in our study is the significant relationship of the number of episodes of olig6-fblock, and duration of oliguria with increased mortality. Although affected by volume status, use of diuretics and other drugs, these associations were seen regardless of the utilization of diuretics and other processes of care elements. These data suggest that closer monitoring of UO and evaluation of the duration and frequency of oliguria could serve as risk markers for adverse events. Defining oliguria on the basis of the total volume of urine in a 6-h interval facilitates the application of the criteria for prospective and retrospective epidemiological studies of AKI. However, in clinical practice, the hourly urine flow provides more precision for risk assessment and establishes early time for interventions. Ideally, it would be preferable to have devices that record UO in real time that display the information with warnings when the UO has decreased below a set threshold.[16]

A key issue is whether UO would provide an earlier indication of renal dysfunction than sCr. As measurements of sCr and UO were not done at the same time intervals, it is difficult to make an exact comparison. While in oliguric AKI patients the difference to reach UO or sCr was not significant, time to reach AKI diagnosis by the UO criterion was shorter than by sCr criteria (Figure 4). However, in a sub-analysis of patients (data not shown) with sCr available every 12 h, the difference in time to reach the criteria was not significant. This fact emphasizes the importance of timed interval samples determining the accuracy of a biomarker. In patients at risk for AKI, more time points for sCr measurements could potentially increase the accuracy of this biomarker.[17] This would need to be determined in future studies. Additionally, as AKI patients are not in steady state and usually exhibit positive fluid balance, the diagnosis of AKI based on sCr may be delayed by 48–72 h, comparing to more sensitive biomarkers of kidney injury.[6–9] The importance of early detection of AKI has been emphasized, as earlier diagnosis would provide a wider window to perform supportive and therapeutic interventions.[18]

Our study has several strengths. We collected data in a prospective manner. The patient population was heterogeneous (women, Hispanics, and African Americans), and we applied UO criteria during the entire ICU stay. However, our study was limited to a single surgical ICU with relatively short length of stay. As baseline sCr prior to hospitalization was not known in all patients, we computed changes using ICU admission sCr as the reference point. Consequently, some patients who had elevated sCr values at admission may have been misclassified as not having AKI based on the sCr criteria. Data regarding the severity of illness was not available, and we could not determine the differences in severity between the three groups of AKI patients (non-oliguric, oliguric with sCr change, and oliguric without sCr change). More importantly, we were unable to determine whether volume status in these patients was optimized first, prior to applying definitions of oliguria to diagnose AKI. Nevertheless, the high incidence of oliguria, its association with adverse outcomes, and the shorter time to AKI diagnosis based on UO criterion highlights the importance of the application of this criterion, regardless of the utilization of diuretics and other processes of care elements.

In conclusion, UO is a sensitive and specific criterion for AKI. Applying both UO and sCr can identify additional patients with AKI compared with the application of sCr criterion alone. Oliguric patients without change in sCr have an increased mortality, increased dialysis requirements, and longer lengths of ICU and hospital stay than patients without AKI. We believe that urine flow rate is a sensitive and specific biomarker that provides an early warning signal for impending renal dysfunction. Coupled with other biomarkers for AKI, urine flow could be used as an early and meaningful diagnostic criterion, and should be included in future studies in AKI.

MATERIALS AND METHODS

The study cohort is derived from patients screened for a multicenter prospective observational study in critically ill patients at risk for AKI between July 2006 and December 2008 at three academic centers (University of California, San Diego, University of Alabama, and Université de Montréal). We analyzed data from a cohort of 317 surgical ICU patients screened at the University of California,

San Diego Medical Center. Patients were screened at ICU admission for potential study participation. Patients were eligible for enrollment if they were aged 18 years or older and had life expectancies of at least 48 h. Patients were excluded if they had AKI according to the AKIN criteria,[11] were admitted to the ICU >48 h prior to screening, transferred from another ICU, had a sCr >177 μmol/l ⩽3 days before ICU admission, were prisoners, received dialysis within the 12 months prior to admission, had a functioning kidney transplant, were on anticoagulants or warfarin within the last 7 days, suffered from decompensated cirrhosis, had chronic kidney disease stage 5, were anemic (hemoglobin <90 g/l or hematocrit <27%) or were already enrolled in another research project. The Institutional Review Board approved a retrospective analysis of all patients screened for the study, and a waiver of individual authorization for use of Protected Health Information was granted as stipulated by the Health Insurance Portability and Accountability Act rules.

We recorded demographic data, co-morbidities, clinical history, and lab studies from the day of ICU admission until ICU discharge. sCr was available at least once per 24 h. We applied the AKIN criteria to define AKI by sCr (creatinine change ⩾0.3 mg/dl or ⩾50% from reference within 48 h). We considered the first sCr measured at ICU admission as the reference sCr. We computed daily and cumulative fluid balance for each patient; however, we did not record details of the type and duration of fluid administration or use of diuretics and other medications.

We classified patients by three different definitions of oliguria on a 6-h time interval (Table 1). Each of these oliguria definitions was compared with AKIN sCr criteria for diagnosing AKI. The oliguria duration over ICU stay was assessed by the number of olig6-fblock episodes and by the total number of hours during which the patient had a urine volume <0.5 ml/kg during the ICU stay. We classified patients at time of diagnosis as oliguric or non-oliguric. Patients reaching oliguria diagnosis before elevation of sCr were classified as being diagnosed by oliguria criterion, and those reaching sCr criterion first were classified as non-oliguric at diagnosis. We additionally assessed the maximum stage reached throughout the course of ICU stay. On the basis of this maximum AKIN stage (either UO or sCr), we stratified patients on one of three categories: non-AKI, non-oliguric AKI, oliguric with sCr change (Type A), and oliguric without sCr change (Type B). Patients with no AKI by either criterion were compared with non-oliguric AKI and with Type A (with sCr changes) and B (without sCr changes) oliguric patients. We compared demographics and risk factors for AKI in these groups of patients. We assessed the rate of progression to more severe stages of AKI, need of renal replacement therapy, length of ICU, and ICU mortality in these patients by AKI diagnosis. We calculated the time to reach AKI diagnosis from ICU admission by oliguria and by sCr criteria. In Type A oliguric AKI patients, the time to reach the criteria was compared.

Statistical analyses

Continuous variables were expressed as mean ± s.d. and analyzed by unpaired Student's *t*-test, or Wilcoxon rank-sum test, as appropriate. Non-parametric variables were expressed as median and 25–75 percentiles and analyzed by Mann–Whitney's test. Categorical variables were analyzed by Pearson's two-test or Fisher's exact test, whenever appropriate. The predictive value of UO on AKI diagnosis was performed using a receiver operator characteristic curve, and the area under the curve was computed. All statistical tests were two-sided, and $P<0.05$ was considered to be significant. A multivariate stepwise logistic regression was used to assess the association of AKI diagnosis and mortality. We evaluate the association of AKI diagnosis using only sCr criterion and including UO criterion. We adjusted the association of AKI diagnosis and mortality for age, cumulative fluid balance (from ICU admission to the day of AKI diagnosis by UO or sCr), sepsis, and need for mechanical ventilation. Statistical analyses were conducted using SPSS 17.0 (Chicago, IL).

DISCLOSURE

All the authors declared no competing interests.

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