Value of Kidney Disease Improving Global Outcomes Urine Output Criteria in Critically Ill Patients: A Secondary Analysis of a Multicenter Prospective Cohort Study

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Abstract

Background: Urine output (UO) is an essential criterion of the Kidney Disease Improving Global Outcomes (KDIGO) definition and classification system for acute kidney injury (AKI), of which the diagnostic value has not been extensively studied. We aimed to determine whether AKI based on KDIGO UO criteria ($KDIGO_{UO}$) could improve the diagnostic and prognostic accuracy, compared with KDIGO serum creatinine criteria ($KDIGO_{SCr}$).

Methods: We conducted a secondary analysis of the database of a previous study conducted by China Critical Care Clinical Trial Group (CCCCTG), which was a 2-month prospective cohort study (July 1, 2009 to August 31, 2009) involving 3063 patients in 22 tertiary Intensive Care Units in Mainland of China. AKI was diagnosed and classified separately based on $KDIGO_{UO}$ and $KDIGO_{SCr}$. Hospital mortality of patients with more severe AKI classification based on $KDIGO_{UO}$ was compared with other patients by univariate and multivariate regression analyses.

Results: The prevalence of AKI increased from 52.4% based on $KDIGO_{SCr}$ to 55.4% based on $KDIGO_{SCr}$ combined with $KDIGO_{UO}$. $KDIGO_{UO}$ also resulted in an upgrade of AKI classification in 7.3% of patients, representing those with more severe AKI classification based on $KDIGO_{UO}$. Compared with non-AKI patients or those with

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Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.189059

Received: 26-04-2016 **Edited by:** Xin Chen
How to cite this article: Qin JP, Yu XY, Qian CY, Li SS, Qin TH, Chen EZ, Lin JD, Ai YH, Wu DW, Liu DX, Sun RH, Hu ZJ, Cao XY, Zhou FC, He ZY, Zhou LH, An YZ, Kang Y, Ma XC, Zhao MY, Jiang L, Xu Y, Du B, for the China Critical Care Clinical Trial Group (CCCCTG). Value of Kidney Disease Improving Global Outcomes Urine Output Criteria in Critically Ill Patients: A Secondary Analysis of a Multicenter Prospective Cohort Study. Chin Med J 2016;129:2050-7.

maximum AKI classification by $KDIGO_{SCr}$, those with maximum AKI classification by $KDIGO_{UO}$ had a significantly higher hospital mortality of 58.4% (odds ratio [*OR*]: 7.580, 95% confidence interval [*CI*]: 4.141–13.873, $P < 0.001$). In a multivariate logistic regression analysis, AKI based on $KDIGO_{UO}$ (*OR*: 2.891, 95% *CI*: 1.964–4.254, $P < 0.001$), but not based on $KDIGO_{SCr}$ (*OR*: 1.322, 95% *CI*: 0.902–1.939, $P = 0.152$), was an independent risk factor for hospital mortality.

Conclusion: UO was a criterion with additional value beyond creatinine criterion for AKI diagnosis and classification, which can help identify a group of patients with high risk of death.

Key words: Acute Kidney Injury; Critically Ill; Mortality; Serum Creatinine; Urine Output

Introduction

Acute kidney injury (AKI) is one of the most common complications in critically ill patients. However, a wide range of prevalence and mortality rates of AKI have been reported in literature, mainly due to different diagnostic criteria of acute renal failure/AKI and the heterogeneity of patient population.[1-4] Hence, the Acute Dialysis Quality Initiative group proposed a graded definition of AKI, the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria in 2004.[5] Three years later, a modified classification scheme from RIFLE, Acute Kidney Injury Network (AKIN) criteria, was developed by the AKIN group in order to improve the diagnostic sensitivity and specificity of AKI.[6] The latest classification system was proposed by the Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, based on the previous two classification systems, with the aim of unifying AKI definition.[7] A large body of evidence has been accumulated and suggested that the development and severity of AKI are associated with increased hospital mortality.[8-16] Despite the difference in creatinine/glomerular filtration rate (GFR) criteria between AKIN, RIFLE, and KDIGO criteria, all use urine output (UO) for the diagnosis and classification of AKI.[5-7] Unfortunately, hourly UO measurements are not always available even among critically ill patients in Intensive Care Unit (ICU). Furthermore, UO may be affected by volume status and diuretic use. As a result, the prognostic value of UO criteria has not been extensively studied as serum creatinine (SCr) criteria. Almost 70% of relevant studies have not employed UO criteria for AKI diagnosis and/or classification,[9-12,17] and some studies have demonstrated that UO criteria might help to define the worst AKI stage in no more than 13% of patients with AKI.[18-20] In addition, creatinine criteria in the consensus definition were proposed based on more solid evidence, while the consensus of UO criteria was mostly arrived through expert opinion. As a consequence, conflicting results have been reported about the role of UO criteria in AKI diagnosis and classification.

We hereby conducted a secondary analysis of a database of a multicenter prospective cohort study in order to test the hypothesis that KDIGO urine output criteria ($KDIGO_{UO}$) may help to improve the diagnostic and prognostic value of AKI, and patients who met $KDIGO_{UO}$ without significant changes in SCr levels had a higher hospital mortality rate.

Methods

Subject enrollment

This study was a secondary analysis of the database of a previous study conducted by China Critical Care Clinical Trial Group (CCCCTG), which was a 2-month prospective cohort study (July 1, 2009 to August 31, 2009) involving 3063 patients in 22 tertiary ICUs in the Mainland of China.[21] The study was approved by the Institutional Review Boards of Fuxing Hospital and granted a waiver of informed consent due to the observational nature of the study. Inclusion criteria in the current study included: (1) Age ≥18 years old, (2) ICU length of stay (LOS) ≥24 h, and (3) at least two SCr measurements were available in a 7-day time window during the first 28 days in ICU. We excluded those patients who had already received chronic dialysis or renal transplantation for end-stage renal disease prior to this ICU admission and those patients with incomplete clinical data.

Data collection and measurements

For every enrolled patient, demographic data, underlying diseases, severity of illness, admission status, laboratory findings, complications, intervention and treatment during ICU stay, and patient outcome were extracted from the database. The severity of illness, including Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score, was assessed based on the worst variables recorded during the first 24 h of ICU admission.[22,23] Severe sepsis and septic shock at ICU admission or during ICU stay were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus definitions.[24] Acute lung injury and acute respiratory distress syndrome (ARDS) were defined according to the American-European Consensus Conference criteria.[25] Chronic renal insufficiency was defined as GFR <60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ according to the Kidney Disease Outcomes Quality Initiative criteria.[26]

Diagnosis and classification of acute kidney injury

AKI was diagnosed and staged according to KDIGO definition and classification system,[7] i.e., both SCr and UO criteria, based on clinical data during the first 28 days during ICU stay. With regards to SCr criteria, AKI was diagnosed in terms of a process of results in a 50% increase in SCr within 1 week or a 3 mg/L (26.5 μmol/L) increase within 48 h. Patient's body weight used in UO criteria was either estimated or measured according to the routine clinical practice of individual ICU. All patients were further classified according to KDIGO SCr ($KDIGO_{SCr}$) or

$KDIGO_{UO}$ criteria only. In particular, AKI was staged over the entire episode, based on the maximal SCr increase during the study period. For example, if a patient developed a 50% increase in SCr in 5 days but ultimately had a three-fold increase over 3 weeks, he or she would be diagnosed with AKI and ultimately staged as stage 3. Given the objective of the current study, those patients receiving renal replacement therapy (RRT) were classified according to $KDIGO_{SCr}$ or $KDIGO_{UO}$ criteria rather than assigned to AKI stage 3 based on KDIGO criteria.[7]

In order to examine the clinical significance of UO criteria, we classified patients with AKI into three groups according to the diagnostic consistency of $KDIGO_{SCr}$ and $KDIGO_{UO}$, i.e., those whose $KDIGO_{SCr}$ stage was more severe than $KDIGO_{UO}$ stage (Group A), those whose $KDIGO_{SCr}$ stage was consistent with $KDIGO_{UO}$ stage (Group B), and those whose $KDIGO_{SCr}$ stage was less severe than $KDIGO_{UO}$ stage (Group C).

Outcome measures

All enrolled patients were followed up until discharge from the current hospital admission, death during the current hospital admission, or 3 months after study entry, whichever occurred earlier. The primary outcome was all-cause hospital mortality. Patients who were still in hospital on November 30, 2009 were deemed survivors.

Statistical analysis

Continuous data were reported as median (Q_1, Q_3) and compared with Mann-Whitney *U*-test or Kruskal-Wallis test. Categorical variables were expressed as proportions and compared with Chi-square test or Fisher's exact test. The predictive value of $KDIGO_{SCr+UO}$ for hospital mortality was examined by multivariate logistic regression analysis. Variables including demographics, comorbidities, severity of illness, admission status, and complications were added into the model using stepwise conditional forward entry, if $P < 0.10$ in univariate analysis. The agreement between $KDIGO_{SCr}$ and $KDIGO_{UO}$ was evaluated with Cohen's kappa coefficient. The second multivariate logistic regression model was constructed to explore the relative influence of $KDIGO_{SCr}$ and $KDIGO_{UO}$ on hospital mortality as the dependent variable in addition to other covariates. Collinearity was analyzed by assessing the correlation between $KDIGO_{SCr}$ and $KDIGO_{UO}$. The predictive value of $KDIGO_{SCr}$ and $KDIGO_{UO}$ was analyzed with an area under the receiver operating curve (AuROC). In order to further delineate the predictive value of $KDIDG_{UO}$ criteria, we also constructed the third multivariate regression model, including AKI status (i.e., non-AKI, Group A, Group B, and Group C) as an independent variable for hospital mortality. Kaplan-Meier survival analysis was used to compare 90-day mortality. The log-rank statistic was used to test the difference between the above groups. All comparisons were unpaired, and all tests of significance were two-tailed. A $P < 0.05$ was considered as statistically significant. All statistical analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA) or MedCalc 11.4 (MedCalc Software bvba, Oostende, Belgium).

Results

General information

Of the 3063 patients who were screened during the 2-month period in the original study, 2005 patients were excluded from the current study. Reasons for exclusion were ICU LOS <24 h ($n = 1623$), fewer than two SCr measurements during ICU stay ($n = 182$), age <18 years ($n = 127$), chronic dialysis and/or renal transplant recipient ($n = 30$), and incomplete clinical data ($n = 43$). As a result, 1058 patients were finally included for analysis [Figure 1].

The patients in the cohort under analysis had a median age of 62 years (45 years, 74 years), and 677 (64.0%) were male. Median APACHE II score was 18 (13, 23), and median SOFA score was 6 (4, 9). A total of 729 patients (68.9%) were admitted into ICU due to medical diseases, while respiratory disorders were the most common reason for ICU admission. There were 222 nonsurvivors, among whom 183 died in ICU, and the other 39 died in general wards, corresponding to ICU mortality and hospital mortality of 17.3% and 21.0%, respectively [Table 1].

Acute kidney injury defined by Kidney Disease Improving Global Outcomes serum creatinine criteria and urine output criteria

Using $KDIGO_{SCr+UO}$ criteria within the first 28 days of ICU admission, AKI occurred in 586 patients (55.4%), with 238 (22.5%) in stage 1, 154 (14.6%) in stage 2, and 194 (18.3%) in stage 3. Compared with patients without AKI, patients with AKI were older, had a higher burden of comorbidities (such as hypertension, diabetes, and chronic renal insufficiency), and higher overall severity of illness scores (such as APACHE II score and SOFA score). Moreover, patients with AKI were more likely to develop complications (such as septic shock and ARDS) and require

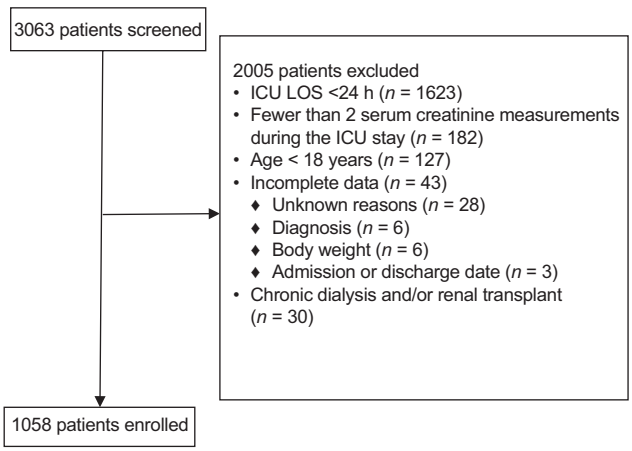

Figure 1: Patient flow chart illustrating enrollment of the study population. ICU: Intensive Care Unit; LOS: Length of stay.

Table 1: Univariate analysis of patient's characteristics in this study

Variables	All Patients (n = 1058)	Non-AKI (n = 472)	Any AKI (n = 586)	P (non-AKI vs. AKI)	AKI (n = 586)			P
					Group A (n = 416)	Group B (n = 93)	Group C (n = 77)	
Male, n (%)	677 (64.0)	297 (62.9)	380 (64.8)	0.517	269 (64.7)	64 (68.8)	47 (61.0)	0.566
Age (years), median (Q_1, Q_3)	62 (45, 74)	59 (41, 73)	65 (46, 75)	<0.001	63 (45, 73)	68 (52, 80)	71 (56, 81)	<0.001
Body weight (kg), median (Q_1, Q_3)	65 (56, 70)	65 (57, 70)	65 (56, 70)	0.722	65 (59, 70)	65 (59, 75)	61(55, 70)	0.129
APACHE II score, median (Q_1, Q_3)	18 (13, 23)	14 (10, 19)	20(16, 26)	<0.001	19 (15, 25)	25 (19, 32)	22(16, 30)	<0.001
SOFA on admission, median (Q_1, Q_3)	6 (4, 9)	5 (3, 7)	8 (5, 10)	<0.001	7 (5, 10)	9 (6, 14)	8 (5, 11)	<0.001
Comorbidities, n (%)								
None	439 (41.5)	227 (48.1)	212 (36.2)	<0.001	165 (39.7)	27 (29.6)	20 (26.0)	0.021
CHD	195 (18.4)	83 (17.6)	112 (19.1)	0.524	66 (15.9)	21 (22.6)	25 (32.5)	0.002
Hypertension	351 (33.2)	133 (28.2)	218 (37.2)	0.002	142 (34.1)	40 (43.0)	36 (46.8)	0.049
Diabetes	169 (16.0)	62 (13.1)	107 (18.3)	0.024	76 (18.3)	15 (16.1)	16 (20.8)	0.737
COPD	111 (10.5)	45 (9.5)	66 (11.3)	0.362	36 (8.7)	13 (14.0)	17 (22.1)	0.002
Solid tumor	122 (11.5)	50 (10.6)	72 (12.3)	0.391	48 (11.5)	12 (12.9)	12 (15.6)	0.599
CKI	51 (4.8)	6 (1.3)	45 (7.7)	<0.001	25 (6.0)	11 (11.8)	9 (11.7)	0.060
Admission status, n (%)								
Medical	729 (68.9)	288 (61.0)	441 (75.3)	<0.001	306 (73.6)	77 (82.8)	58 (75.3)	0.175
Elective surgery	192 (18.1)	126 (26.7)	66 (11.3)	<0.001	46 (11.1)	10 (10.8)	10 (13.0)	0.873
Emergency surgery	137 (12.9)	58 (12.3)	79 (13.5)	0.566	64 (15.4)	6 (6.5)	9 (11.7)	0.066
Reasons for ICU admission, n (%)								
Respiratory	367 (34.7)	154 (32.6)	213 (36.3)	0.206	144 (34.6)	31 (33.3)	38 (49.4)	0.038
Gastrointestinal	198 (18.7)	101 (21.4)	97 (16.6)	0.045	72 (17.3)	16 (17.2)	9 (11.7)	0.468
Neurological	161 (15.2)	78 (16.5)	83 (14.2)	0.288	71 (17.1)	5 (5.4)	7 (9.1)	0.005
Cardiovascular	133 (12.6)	49 (10.4)	84 (14.3)	0.054	55 (13.2)	16 (17.2)	13 (16.9)	0.484
Trauma	108 (10.2)	58 (12.3)	50 (8.5)	0.045	39 (9.4)	6 (6.5)	5 (6.5)	0.521
Renal	46 (4.3)	4 (0.8)	42 (7.2)	<0.001	20 (4.8)	18 (19.4)	4 (5.2)	<0.001
Other	45 (4.3)	28 (5.9)	17 (2.9)	0.015	15 (3.6)	1 (1.1)	1 (1.3)	0.281
On ICU admission, median (Q_1, Q3)								
Creatinine (μmol/L)	77.0 (56.0, 112.0)	66.0 (51.0, 82.0)	95.5 (62.0, 152.0)	<0.001	92.0 (62.0, 134.0)	132.0 (75.0, 390.0)	92.0 (59.5, 181.0)	<0.001
Urine output (ml)	2000 (1400, 2800)	2200 (1569, 3000)	1900 (1185, 2704)	<0.001	2178 (1500, 3000)	1000 (299, 1700)	1350 (557, 2008)	<0.001
Interventions during ICU stay, n (%)								
Mechanical ventilation	798 (75.4)	322 (68.2)	476 (81.2)	<0.001	328 (78.8)	81 (87.1)	67 (87.0)	0.069
Vasopressor	406 (38.4)	99 (21.0)	307 (52.4)	<0.001	183 (44.0)	73 (78.5)	51 (66.2)	<0.001
RRT	135 (12.8)	18 (3.8)	117 (20.0)	<0.001	43 (10.3)	54 (58.1)	20 (26.0)	<0.001
Diuretics	539 (50.9)	173 (36.7)	366 (62.5)	<0.001	232 (55.8)	78 (83.9)	56 (72.7)	<0.001
Complication, n (%)								
ICU-acquired infection	121 (11.4)	43 (9.1)	78 (13.3)	0.033	65 (15.6)	9 (9.7)	4 (5.2)	0.025
Severe sepsis/septic shock	412 (38.9)	127 (26.9)	285 (48.6)	<0.001	179 (43.0)	59 (63.4)	47 (61.0)	<0.001
ALI/ARDS	490 (46.3)	159 (33.7)	331 (56.5)	<0.001	219 (52.6)	64 (68.8)	48 (62.3)	0.009
Clinical outcome								
ICU mortality, n (%)	183 (17.3)	32 (6.8)	151 (25.8)	<0.001	66 (15.9)	46 (49.5)	39 (50.6)	<0.001
Hospital mortality, n (%)	222 (21.0)	44 (9.3)	178 (30.4)	<0.001	85 (20.4)	48 (51.6)	45 (58.4)	<0.001
ICU LOS (days), median (Q_1, Q_3)	6 (3, 12)	4 (3, 7)	8 (4, 17)	<0.001	9 (4, 18)	8 (4, 18)	6 (3, 13)	0.026
Hospital LOS (days), median (Q_1, Q_3)	22 (12, 42)	22 (12, 39)	23 (12, 45)	0.036	24 (12, 47)	22 (11, 39)	20 (9, 43)	0.931

Group A: KDIGOSCr stage more severe than KDIGOUO stage; Group B: KDIGOSCr stage consistent with KDIGOUO stage; Group C: KDIGOSCr stage less severe than KDIGOUO stage; AKI: Acute kidney injury; APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: Acute respiratory distress syndrome; CHD: Coronary heart disease; CKI: Chronic kidney insufficiency; COPD: Chronic obstructive pulmonary disease; ICU: Intensive Care Unit; IQR: Interquartile range; KDIGO: Kidney Disease Improving Global Outcomes; KDIGOSCr: KDIGO serum creatinine criteria; KDIGOUO: KDIGO urine output criteria; LOS: Length of stay; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment.

interventions including vasopressors, mechanical ventilation, diuretics, and RRT [Table 1].

Compared with patients without AKI, patients with AKI had a higher ICU mortality (25.8% vs. 6.8%, $P < 0.001$) and hospital mortality (30.4% vs. 9.3%, $P < 0.001$). In multivariate logistic regression, AKI was an independent risk factor for hospital mortality (odds ratio [*OR*]: 2.326, 95% confidence interval [*CI*]: 1.574–3.437, $P < 0.001$).

Acute kidney injury diagnosis and classification by Kidney Disease Improving Global Outcomes urine output criteria versus Kidney Disease Improving Global Outcomes serum creatinine criteria

Among the 1058 enrolled patients, 554 patients with AKI (52.4%) could be diagnosed by $KDIGO_{SCr}$ alone, whereas the other 32 AKI patients (3.0%) were identified only by $KDIGO_{UO}$. Agreement between $KDIGO_{SCr}$ and $KDIGO_{UO}$ in the diagnosis of AKI versus non-AKI was poor as suggested by Cohen's kappa coefficient of 0.255 (95% *CI*: 0.211–0.300).

$KDIGO_{UO}$ also exerted a significant impact on AKI classification. According to $KDIGO_{SCr}$ alone, 504 (47.6%), 257 (24.3%), 148 (14.0%), and 149 (14.1%) patients were classified as non-AKI, AKI stages 1, 2, and 3, respectively [Table 2]. However, the use of UO criteria would result in upgrade of AKI classification in 77 patients (7.3%), including 32 patients upgraded from $KDIGO_{SCr}$ non-AKI to $KDIGO_{UO}$ AKI stage 1 ($n = 12$), stage 2 ($n = 8$), and stage 3 ($n = 12$), 31 patients upgraded from $KDIGO_{SCr}$ stage 1 to $KDIGO_{UO}$ stage 2 ($n = 12$) and stage 3 ($n = 19$), and 14 patients upgraded from $KDIGO_{SCr}$ stage 2 to $KDIGO_{UO}$ stage 3. Agreement between $KDIGO_{SCr}$ and $KDIGO_{UO}$ for AKI classification was also poor (Cohen's kappa coefficient of 0.312, 95% *CI*: 0.265–0.359).

Acute kidney injury prognosis by Kidney Disease Improving Global Outcomes urine output criteria versus Kidney Disease Improving Global Outcomes serum creatinine criteria

As expected, hospital mortality significantly increased with increasing severity of AKI, regardless of criteria for AKI staging (i.e., $KDIGO_{SCr+UO}$, $KDIGO_{SCr}$, or $KDIGO_{UO}$) [Table 3]. However, the predictive values of $KDIGO_{SCr}$ and $KDIGO_{UO}$ classification were comparable, with AuROC of 0.666 (95% *CI*: 0.637–0.694) and 0.678 (95% *CI*: 0.649–0.706), respectively ($P = 0.579$).

In multivariate logistic regression analysis, AKI based on $KDIGO_{UO}$ ($KDIGO_{UO}$ AKI; *OR*: 2.891, 95% *CI*: 1.964–4.254, $P < 0.001$), but not based on $KDIGO_{SCr}$ ($KDIGO_{SCr}$ AKI; *OR*: 1.322, 95% *CI*: 0.902–1.939, $P = 0.152$), was an independent risk factor for hospital mortality, after adjusting for other potential confounders [Table 4]. No collinearity had been found with either $KDIGO_{SCr}$ AKI or $KDIGO_{UO}$ AKI, with variance inflation factor of 1.306 and 1.408, respectively. We did not find any interaction between $KDIGO_{UO}$ AKI and $KDIGO_{SCr}$ AKI ($P = 0.125$).

Among the 586 patients with AKI, there were 416 patients (71.0%) in Group A (i.e., $KDIGO_{SCr}$ stage was more severe than $KDIGO_{UO}$ stage), 93 patients (15.9%) in Group B (i.e., $KDIGO_{SCr}$ stage was consistent with $KDIGO_{UO}$ stage), and 77 patients (13.1%) in Group C (i.e., $KDIGO_{SCr}$ stage was less severe than $KDIGO_{UO}$ stage). These patients differed significantly with regards to age, comorbidities, severity of illness, renal function on ICU admission, and hospital mortality [Table 1]. Multivariate logistic regression analysis showed that compared with non-AKI, patients in group B (*OR*: 3.916, 95% *CI*: 2.201–6.968, $P < 0.001$) and group C (*OR*: 7.580, 95% *CI*: 4.141–13.873, $P < 0.001$) had a significantly higher risk of hospital mortality, whereas patients in group A had a similar hospital mortality [Table 4]. These findings were also confirmed by Kaplan-Meier survival curve [Figure 2].

Discussion

The current study showed that AKI as defined by KDIGO definition and classification system was common (55.4%) among critically ill patients, with a hospital mortality of 30.4%. In addition to $KDIGO_{SCr}$ alone, use of $KDIGO_{UO}$ could identify an additional 3.0% of patients as having AKI and result in a change of AKI stage in 7.3% patients. Furthermore, $KDIGO_{UO}$ had a better predictive value for hospital mortality than $KDIGO_{SCr}$.

There were wide variations in the reported prevalence of AKI (5.7–74.5%) in different studies, possibly due to different study designs, heterogeneity of patient population, different diagnostic criteria, and determination of baseline creatinine levels.[4,8,12,15,18,19,27-32] In a recent cohort study involving 32,045 ICU patients, Kellum *et al*.[31] reported an AKI prevalence of 74.5% based on KDIGO criteria. However, in a retrospective analysis of prospectively collected data by Bagshaw *et al*.,[19] AKI occurred in 36.1% of 120,123 ICU patients. Likewise, Joannidis *et al*.[15] reported an AKI prevalence of 35.5% among 16,784 patients from 303 ICUs in a cohort analysis of SAPS 3 database. The latter two large studies, based on SCr and UO data within the first 24 or 48 h after ICU admission, reported the prevalence of AKI that was much lower than that of our study.

In the 1058 critically ill patients in our study, 32 (3.0%) patients without significant SCr change were diagnosed as AKI based on $KDIGO_{UO}$, similar to 4.8% as reported

Table 2: Cross tabulation of patients classified by $KDIGO_{SCr}$ criteria versus $KDIGO_{UO}$ criteria

$KDIGO_{SCr}$	$KDIGO_{UO}$				
	No AKI	AKI stage 1	AKI stage 2	AKI stage 3	Total
No AKI	472	12	8	12	504
AKI stage 1	208	18	12	19	257
AKI stage 2	106	17	11	14	148
AKI stage 3	59	13	13	64	149
Total	845	60	44	109	1058

Numbers of patients classified into the respective stages of AKI by $KDIGO_{SCr}$ or $KDIGO_{UO}$ are cross-tabulated against each other. AKI: Acute kidney injury; KDIGO: Kidney Disease Improving Global Outcomes; $KDIGO_{SCr}$: KDIGO serum creatinine criteria; $KDIGO_{UO}$: KDIGO urine output criteria.

Table 3: Hospital mortality of AKI stages according to KDIGO criteria by univariate analysis

KDIGO stage	KDIGOSCr + UO				KDIGOUO alone				KDIGOSCr alone			
	Total, *n*	Mortality, *n* (%)	*OR* (95% *CI*)	*P*	Total, *n*	Mortality, *n* (%)	*OR* (95% *CI*)	*P*	Total, *n*	Mortality, *n* (%)	*OR* (95% *CI*)	*P*
No AKI	472	44 (9.3)	Reference		845	118 (14.0)	Reference		504	60 (11.9)	Reference	
AKI stage 1	238	43 (18.1)	2.145 (1.363–3.375)	0.001	60	18 (30.0)	2.640 (1.470–4.742)	0.001	257	56 (21.8)	2.062 (1.381–3.077)	<0.001
AKI stage 2	154	42 (27.3)	3.648 (2.277–5.843)	<0.001	44	18 (40.9)	4.265 (2.268–8.022)	<0.001	148	44 (29.7)	3.131 (2.009–4.879)	<0.001
AKI stage 3	194	93 (47.9)	8.957 (5.890–13.619)	<0.001	109	68 (62.4)	10.218 (6.623–15.765)	<0.001	149	62 (41.6)	5.274 (3.455–8.049)	<0.001

AKI: Acute kidney injury; KDIGO: Kidney Disease Improving Global Outcomes; KDIGOSCr: KDIGO serum creatinine criteria; KDIGOUO, KDIGO urine output criteria; KDIGOSCr + UO: KDIGO serum creatinine criteria and urine output criteria; OR: Odds ratio; CI: Confidence interval.

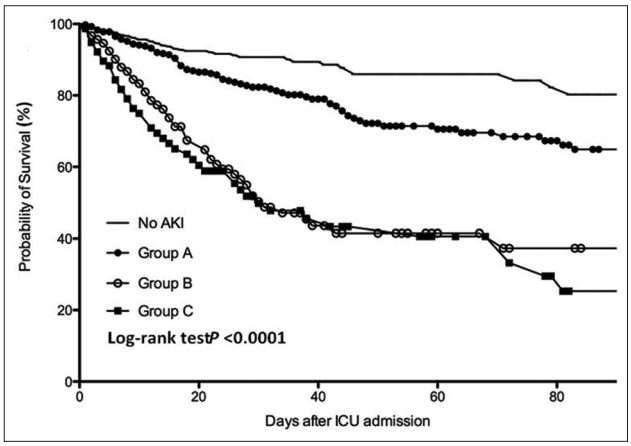

Figure 2: Kaplan-Meier survival curves from ICU admission to 90 days. Group A: $KDIGO_{SCr}$ stage more severe than $KDIGO_{UO}$ stage; Group B: $KDIGO_{SCr}$ stage consistent with $KDIGO_{UO}$ stage; Group C: $KDIGO_{SCr}$ stage less severe than $KDIGO_{UO}$ stage. AKI: Acute kidney injury; ICU: Intensive Care Unit; KDIGO: Kidney Disease Improving Global Outcomes; $KDIGO_{SCr}$: KDIGO serum creatinine criteria; $KDIGO_{UO}$: KDIGO urine output criteria.

by Joannidis *et al*.[15] Moreover, in 77 out of 586 AKI patients (13.1%) in the current study, it was the $KDIGO_{UO}$ that led to a worse AKI class, which was also consistent with the findings (13%) of Cruz *et al*.[18] In contrast, in a prospective observational study, the prevalence of AKI increased from 24%, based solely on SCr, to 52% by adding the UO as a diagnostic criterion.[32] This might be explained by the difference in patient population. Compared with our study, patients in the above study were less severely ill, as suggested by younger age, fewer patients with severe sepsis (12.6% vs. 38.9%) and mechanical ventilation (45.4% vs. 75.4%), as well as lower hospital mortality (5.7% vs. 21.0%).[33] However, patient characteristics in studies by Joannidis *et al*.[15] and Cruz *et al*.[18] were comparable to our study, with regards to age (63.0 years vs. 64.3 years vs. 62.0 years), male (59.2% vs. 62.2% vs. 64.0%), medical admissions (76.0% vs. 72.2% vs. 68.9%), and mortality rate of AKI patients (36.4% vs. 36.3% vs. 30.4%). It was intuitive that severely ill patients were more likely to have decreased GFR and increased SCr level, which might compromise the diagnostic value of UO criteria. All these might indicate that UO criteria might help improve diagnostic sensitivity in mild-to-moderately ill patients. Poor agreement either between $KDIGO_{SCr}$ and $KDIGO_{UO}$ with regards to the diagnosis and classification of AKI further suggested less validity of SCr monitoring in this cohort and the complexity of UO in different clinical settings.

Our study also suggested that $KDIGO_{UO}$ might exert a better prognostic value than $KDIGO_{SCr}$. In a retrospective analysis of a high-resolution database of 14,524 patients admitted to 7 ICUs between 2001 and 2007, UO outperformed creatinine as a better mortality predictor than creatinine alone or the combination of both in patients who developed AKI.[34] In clinical practice, UO monitoring might exhibit some advantages over SCr measurements as an early warning sign of deteriorating renal function without the need for blood sampling.[34,35] Nevertheless, conflicting results had also been reported. For example, with the use of multivariate logistic regression analysis, RIFLE classification based on both SCr and UO criteria was the strongest predictor of ICU mortality, while diuresis was not significantly associated with mortality ($P = 0.058$).[18] In a prospective study of 282 cardiac surgery patients, creatinine-based RIFLE or AKIN classes were the strongest predictors of hospital mortality, whereas the UO criteria showed the lowest predictive value.[36] Ricci *et al*.,[16] in a systematic review in 2008, found that the relative risk for death appeared to be higher when only the creatinine criteria were used. The exact reason for the conflicting results remained unclear. UO was neither sensitive nor specific marker of renal function.[37,38] For example, a decrease of GFR might be associated with impaired ability to concentrate urine; therefore without significant decrease of UO, on the other hand, a nonsustained decrease of UO could simply represent a physiological renal adaptation to maintain the body volume and/or electrolytes homeostasis.[38] Therefore, the better prognostic value of $KDIGO_{UO}$ observed in our study might be explained by the fact that decreased UO not only reflected the deterioration of renal function but also suggested tissue hypoperfusion. In fact, studies demonstrated that increase in SCr was more common in patients with oliguria accompanied by hemodynamic compromise (hypotension, tachycardia, or increasing vasopressor and/or inotrope dose).[37]

Table 4: Risk factors for hospital mortality by multivariate logistic regression analysis

Variables	Model 1*		Model 2†	
	OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
APACHE II score	1.107 (1.081–1.135)	<0.001	1.109 (1.082–1.136)	<0.001
Comorbidity				
Solid tumor	2.367 (1.473–3.806)	<0.001	2.302 (1.424–3.721)	0.001
Complications				
Severe sepsis/septic shock	1.821 (1.282–2.587)	0.001	1.849 (1.299–2.631)	0.001
AKI diagnosis				
Non-AKI	Reference		Reference	
$KDIGO_{SCr}$ AKI	1.322 (0.902–1.939)	0.152		
$KDIGO_{UO}$ AKI	2.891 (1.964–4.254)	<0.001		
AKI classification				
AKI Group A			1.591 (1.045–2.421)	0.030
AKI Group B			3.916 (2.201–6.968)	<0.001
AKI Group C			7.580 (4.141–13.873)	<0.001

*Covariates included in multivariate logistic regression model included AKI diagnosis based on $KDIGO_{SCr}$ or $KDIGO_{UO}$, and all variables with $P<0.1$ in univariate analysis, such as gender, age, APACHE II score, SOFA score, comorbidities (no comorbidities, hypertension, chronic obstructive pulmonary disease, solid tumor, chronic kidney insufficiency), admission status (medical, elective surgery, emergency surgery), reasons of ICU admission (respiratory, gastrointestinal, trauma, and other diseases), renal function on ICU admission (serum creatinine level on ICU admission, urine output during first 24 h after ICU admission), complications (severe sepsis/septic shock, and acute lung injury/acute respiratory distress syndrome); †Covariates included in multivariate logistic regression model included AKI classifications (non-AKI, AKI Group A, B, and C), and all variables with $P<0.1$ in univariate analysis. Group A: $KDIGO_{SCr}$ stage more severe than $KDIGO_{UO}$ stage; Group B: $KDIGO_{SCr}$ stage consistent with $KDIGO_{UO}$ stage; Group C: $KDIGO_{SCr}$ stage less severe than $KDIGO_{UO}$ stage. AKI: Acute kidney injury; APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive Care Unit; KDIGO: Kidney Disease Improving Global Outcomes; $KDIGO_{SCr}$: KDIGO serum creatinine criteria; $KDIGO_{UO}$: KDIGO urine output criteria; SOFA: Sequential Organ Failure Assessment; *OR*: Odds ratio; *CI*: Confidence interval.

Our study had several limitations. First, this was a secondary analysis of prospectively collected data and should be regarded as hypothesis generating rather than hypothesis validating. Second, AKI diagnosis and classification were based on clinical data within the first 28 days of ICU admission, which might underestimate the prevalence and severity of late AKI. However, Mandelbaum *et al*.[34] found that for observation periods longer than 2 days, mortality risk was independent of observation period but related to the severity of SCr increase or oliguria. This might indicate that observation periods exerted little impact, if any, on the prognostic value of creatinine and/or UO in AKI patients. Third, we did not investigate the potential influence of fluid balance, vasopressors, and diuretics on UO. In addition, volume status before AKI diagnosis and classification was not assessed. Last, we did not examine the association between duration of oliguria and a subsequent elevated SCr level.[37]

In conclusion, we demonstrated that in adult patients with ICU LOS more than 24 h, UO provided a criterion with additional value beyond creatinine criterion for AKI diagnosis and classification. Compared with creatinine criterion alone, the application of both UO and creatinine criteria may help identify a group of patients who were oliguric but without significant SCr change. This group of patients, despite only representing 7.3% of the cohort (or 13.1% of patients with AKI), had a similar hospital mortality to patients who were oliguric and with significant SCr change, which was markedly higher than that of non-AKI patients or nonoliguric patients with significant SCr change. Based on the above findings, we believed that UO criteria represent an important element of the KDIGO definition and classification system.

Financial support and sponsorship

The study was supported by a grant from the Capital Clinical Application Research of the Beijing Municipal Science and Technology Commission (No. Z131107002213112).

Conflicts of interest

There are no conflicts of interest.

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