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Redefining urine output thresholds for acute kidney injury criteria in critically Ill patients: a derivation and validation study

Guido Dias Machado[1], Leticia Libório Santos[2] and Alexandre Braga Libório[1*]

Abstract

Introduction The current definition of acute kidney injury (AKI) includes increased serum creatinine (sCr) concentration and decreased urinary output (UO). Recent studies suggest that the standard UO threshold of 0.5 ml/kg/h may be suboptimal. This study aimed to develop and validate a novel UO-based AKI classification system that improves mortality prediction and patient stratification.

Methods Data were obtained from the MIMIC-IV and eICU databases. The development process included (1) evaluating UO as a continuous variable over 3-, 6-, 12-, and 24-h periods; (2) identifying 3 optimal UO cutoff points for each time window (stages 1, 2, and 3); (3) comparing sensitivity and specificity to develop a unified staging system; (4) assessing average versus persistent reduced UO hourly; (5) comparing the new UO-AKI system to the KDIGO UO-AKI system; (6) integrating sCr criteria with both systems and comparing them; and (7) validating the new classification with an independent cohort. In all these steps, the outcome was hospital mortality. Another analyzed outcome was 90-day mortality. The analyses included ROC curve analysis, net reclassification improvement (NRI), integrated discrimination improvement (IDI), and logistic and Cox regression analyses.

Results From the MIMIC-IV database, 35,845 patients were included in the development cohort. After comparing the sensitivity and specificity of 12 different lowest UO thresholds across four time frames, 3 cutoff points were selected to compose the proposed UO-AKI classification: stage 1 (0.2–0.3 mL/kg/h), stage 2 (0.1–0.2 mL/kg/h), and stage 3 (< 0.1 mL/kg/h) over 6 h. The proposed classification had better discrimination when the average was used than when the persistent method was used. The adjusted odds ratio demonstrated a significant stepwise increase in hospital mortality with advancing UO-AKI stage. The proposed classification combined or not with the sCr criterion outperformed the KDIGO criteria in terms of predictive accuracy—AUC-ROC 0.75 (0.74–0.76) vs. 0.69 (0.68–0.70); NRI: 25.4% (95% CI: 23.3–27.6); and IDI: 4.0% (95% CI: 3.6–4.5). External validation with the eICU database confirmed the superior performance of the new classification system.

Conclusion The proposed UO-AKI classification enhances mortality prediction and patient stratification in critically ill patients, offering a more accurate and practical approach than the current KDIGO criteria.

*Correspondence:
Alexandre Braga Libório
alexandreliborio@yahoo.com.br
[1] Medical Sciences Postgraduate Program, Universidade de Fortaleza-UNIFOR, Fortaleza, Ceará, Brazil
[2] Medical Program, Universidade de Fortaleza-UNIFOR, Fortaleza, Ceará, Brazil

Introduction

The current definition and staging of acute kidney injury (AKI) considers alterations in the serum creatinine (sCr) level and urinary output (UO) [1]. The definition of reduced UO can be complex and ideally must encompass (1) physiological concepts where the urine volume should be sufficient to eliminate all necessary

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solutes at maximum urinary concentration; (2) structural injuries detectable by new renal biomarkers; (3) proposed therapies and (4) significant short- and long-term patient outcomes [2]. Although studies have demonstrated the importance of reduced UO, defined by AKI criteria, on severity assessment and patient outcomes even when not accompanied by serum creatinine criteria [3, 4], the threshold of 0.5 ml/kg/h has recently been challenged [2, 5], and studies in critically ill patients have reported an association with mortality only when lower thresholds are present [5–9].

In a larger cohort study conducted in Finland, compared to standard thresholds, stricter (< 0.3 ml/kg/h for 6 h or < 0.1 ml/kg/h for 3 h) cutoffs increased the predictive value of reduced UO for mortality [7]. More recently, based on findings from another large cohort of critically ill patients, a minimum average UO of < 0.2 ml/kg/h for 6 h was suggested as the new threshold to define oliguria [6]. These and other studies raised other caveats on the AKI definition: the duration of reduced urine output (from 3 to 24 h intervals) [4, 6] and, if averaged (total UO in a time window divided by the number of hours) or a persistent (UO below the threshold every hour of the time window) reduction in UO during the time frame must be used [10].

While these studies have suggested that the level of UO is independently associated with significant outcomes, constructing a staging system requires evaluating whether a new model is not only associated with outcomes but also whether it is able to predict outcomes more accurately and better classify patients [11]. To the best of our knowledge, no studies have assessed whether different UO cutoff points across various time windows can create a severity staging system superior to the current one or, moreover, whether this superiority is maintained when combined with the sCr criterion.

In the present study, we attempted to develop and validate a UO staging system for AKI, with hospital mortality as the main outcome. Our approach was sequential: (1) we evaluated the lowest UO volume as a continuous variable over 3, 6, 12, and 24-h periods; (2) for each time window, we selected the three UO cutoffs (stages 1, 2 and 3) that maintained the nearest predictive capacity of UO as a continuous variable; (3) we compared the sensitivity and specificity of each stage from different time windows to develop a unified staging system; (4) this proposed UO-AKI classification was evaluated using average or persistent reduced UO; (5) subsequently, we compared the best selected UO-AKI staging system to the KDIGO UO-AKI system; (6) we compared the proposed and KDIGO systems after adding the sCr criterion to both; and finally, (7) we assessed the superiority of the newly proposed UO/sCr AKI system against the UO/sCr KDIGO system using another independent cohort.

Methods

Data source

We used data from two independent databases—the Medical Information Mart for Intensive Care IV (MIMIC-IV) [12, 13] and the eICU Collaborative Research Database (eICU) [14]—for this study. The MIMIC-IV project is managed by the Massachusetts Institute of Technology Laboratory for Computational Physiology and houses data on patients admitted to Beth Israel Deaconess Medical Center from 2008 to 2019. We used the MIMIC-IV to develop the proposed UO-AKI classification system to compare average and persistent reduced UO definitions and to evaluate the proposed system against the actual KDIGO classification system using discrimination, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) methods [11]. The eICU is a multicenter database comprising deidentified health data from more than 200,000 ICU admissions across the United States during the period of 2014–2015. We used the eICU as an independent external validation tool by comparing the proposed method against the KDIGO classification. The MIMIC-IV and eICU databases are publicly available, and researchers who agree to the data use agreement and have completed "protecting human subjects training" can request access. The MIMIC database was approved by the institutional review boards of the Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (No. 0403000206), which waived the requirement for individual patient consent because the datasets contained deidentified information. Ethics approval of the eICU database was not applicable because it was released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision (HIPAA Certification No. 1031219–2).

Study population

All adult patients (aged > 18 years) admitted to the ICU in both databases were assessed for eligibility. The exclusion criteria were (1) ICU length of stay (LOS) < 24 h or > 28 days; (2) basal SCr > 4 mg/dL (see definition below) or end-stage kidney disease and receiving maintenance kidney replacement therapy (KRT); (3) incomplete ICU data precluding AKI definition and staging (i.e., < 24 h of output fluid measurements or absence of sCr measurement during the ICU stay); and (4) absence of weight records. When patients had multiple ICU admissions, we considered only the first one.

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Data collection

Structured query language was used to extract data from both databases. The data collected from the MIMIC-IV included age, sex, admission body weight, ICU admission type, Charlson comorbidity index, and lowest sCr level recorded within 6 months of ICU admission. During the first 28 days of the ICU stay or until KRT initiation, we collected daily sCr levels, a modified version of the Sequential Organ Failure Assessment (SOFA) [15] score excluding the renal score (nonrenal SOFA), the need for mechanical ventilation or vasoactive drugs, the use of loop diuretics and all UO measurements. Additionally, we recorded the method of UO collection: indwelling urinary catheter, other devices (external urinary catheter, nephrostomy, cystostomy), or spontaneous voiding. Finally, we recorded the need for KRT during the hospital stay and the 90-day mortality rate.

Definitions

The reference baseline sCr level used to diagnose and classify AKI in the first 48 h and 7 days after ICU admission to account for the temporality inherent to the KDIGO sCr criteria (see next section) was defined as the lowest sCr level recorded within 6 months of ICU admission. In the absence of eligible sCr levels measured before ICU admission, we considered the lowest value available during the ICU stay after excluding values measured during KRT and within a period of 3 days after KRT [16]. After 48 h of ICU stay, 48-h and 7-day sliding windows were used to define dynamic baselines. The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [17].

AKI diagnosis and staging according to the sCr criteria

According to the KDIGO criteria [1], AKI was defined as an increase in the sCr level to at least 1.5 times the baseline value within a 7-day period or an increase in the sCr level by at least 0.3 mg/dL within a 48-h time frame. Stage 1 was defined as a peak-to-baseline difference of at least 0.3 mg/dL or a peak-to-baseline ratio of 1.5 to 1.9; stage 2 was defined as a peak-to-baseline ratio of 2.0 to 2.9; and stage 3 was defined as a peak-to-baseline ratio of at least 3.0, an sCr level of at least 4.0 mg/dL or KRT initiation.

Urine output assessment

We constructed an hourly UO table for each patient. No missing UO values were imputed. For missing hourly UO values, we attributed values calculated by dividing the next available value by the number of adjacent hours missing, assuming that the sequence corresponded to consolidated data entry. Then, for each hour, we computed a 3-h mean corresponding to the mean UO measured within the previous 3 h. Similarly, we calculated the 6-, 12- and 24-h means. All values were adjusted to the patient's body weight (units in mL/kg/h).

AKI staging according to urine output

Patients were classified according to the KDIGO criteria: stage 1 AKI was defined as a 6-h mean of less than 0.5 mL/kg/h, stage 2 AKI was defined as a 12-h mean of less than 0.5 mL/kg/h, and stage 3 AKI was defined as a 24-h mean of less than 0.3 mL/kg/h or a 12-h period of anuria. Additionally, patients were classified according to newly derived cutoff points, as explained below—the proposed UO-AKI staging system.

Overall AKI staging

Additionally, we classified the patients according to the highest AKI stage reached by a patient using the sCr criteria and UO criteria (UO/sCr stage).

Outcomes

Our primary outcome was hospital mortality. Additionally, we evaluated kidney-centered outcomes (progression to stage 2/3 sCr-AKI (excluding the need for KRT); stage 3 sCr-AKI, including KRT; and the need for KRT isolation) and 90-day mortality. In the MIMIC-IV, the date of death is extracted from two sources: the hospital information system and the Massachusetts State Registry of Vital Records and Statistics. In the eICU database, only hospital discharge status data were available.

Statistical analysis

Continuous data are reported as the mean ± SD or median [IQR], depending on the data distribution. Continuous variables were compared using unpaired t tests or analysis of variance (ANOVA) for normally distributed data and Mann–Whitney or Kruskal–Wallis tests for nonnormally distributed data. Categorical variables are expressed as numbers (percentages) and were compared using the χ^2 test or Fisher's exact test.

To develop a UO-AKI staging system, we used the MIMIC-IV database. We selected the lowest mean UO in the 3-, 6-, 12-, and 24-h time frames and generated receiver operating characteristic (ROC) curves to evaluate the accuracy for predicting mortality. For each time frame, three cutoff points representing each severity stage were chosen based on the highest Youden index for predicting hospital mortality. To ensure that these points best preserved the area under the curve (AUC-ROC), we tested the AUC-ROC against UO as a continuous variable for each time interval. To construct our UO-AKI classification system, we compared the sensitivity and

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specificity of each point representing stages 1, 2, and 3 of all time frames and selected those with the best Youden index for predicting hospital mortality. For example, for stage 1 of the proposed UO-AKI classification, we compared the cutoff points corresponding to stage 1 from the 3-, 6-, 12-, and 24-h time frames.

After defining the thresholds and time frames of the proposed UO-AKI classification, we classified patients using two methods: (1) the average method, where the minimum average UO was less than the established cutoff for each stage, and (2) the persistent method, where the minimum persistent UO was less than the established cutoff during each hour of the time frame.

After selecting the best proposed classification system, we tested whether each stage was independently associated with in-hospital mortality. Logistic regressions were used to test the association between AKI classification and in-hospital mortality. The strength of the association was measured using odds ratios (ORs) and 95% confidence intervals (CIs). Univariate and multivariate logistic regression analyses were performed to assess the associations after adjusting for several confounders: age, sex, baseline sCr level, Charlson Comorbidity Index, ICU admission type, worst nonrenal SOFA score, and the need for kidney replacement therapy (KRT). Missing data not related to urine output, sCr, weight records or mortality were imputed using multiple imputation. We used the Cox proportional hazards model to plot 90-day survival curves for each AKI stage according to each criterion, adjusting for the confounders cited above.

We tested the proposed classification against KDIGO criteria (both UO and UO/sCr-AKI) using the AUC-ROC curve, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) [11]. The 95% CIs for the NRI and IDI were calculated using bootstrap resampling (n = 1000). Sensitivity analyses were performed considering the use of loop diuretics and baseline eGFR. Finally, we validated the superiority of the proposed UO/sCr AKI classification against KDIGO using another independent database (eICU).

Subgroup analyses were performed to assess whether loop diuretic use or baseline renal function could affect the performance of the proposed AKI criteria compared with the KDIGO criteria. For all analyses, a two-tailed P < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using R, version 4.1.0, and SPSS, version 29.0.2.

Results

Patient characteristics

According to the MIMIC-IV, 50,920 adult patients were admitted to the ICU, and 38,622 had an ICU LOS between 24 h and 28 days. A total of 2,186 patients were excluded because their baseline sCr was greater than or equal to 4 mg/dL or because they were undergoing maintenance KRT; 152 patients had missing baseline sCr; 277 patients had no sCr measurements during their ICU stay; and 162 patients had no weight records. Overall, 35,845 patients remained in the derivation cohort. A flowchart of the inclusion and exclusion criteria for patients from the derivation and validation cohorts is shown in Fig. 1.

The demographic and clinical characteristics of the patients in the derivation cohort according to in-hospital mortality are presented in Table 1. A total of 20,195 patients (56.2%) were male, and the mean age at ICU admission was 65.0 ± 16.9 years. The median nonrenal
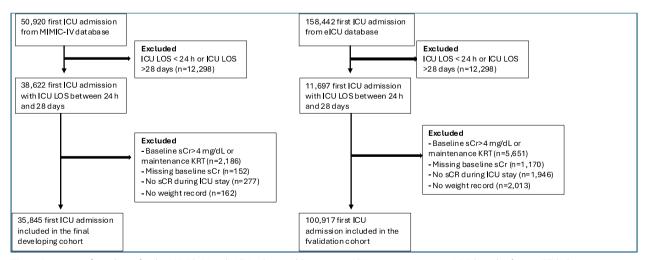

Fig. 1 Participant flow charts for the MIMIC-IV and eICU cohorts. Abbreviations: ICU: intensive care unit; LOS: length of stay; KRT: kidney replacement therapyve; sCr: serum creatinine; eICU:eICU Collaborative Research Database; MIMIC-IV: Medical Information Mart for Intensive Care IV

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Table 1 Patient demographics and characteristics at the first 28 days of ICU stay or up to kidney replacement therapy initiation from the developing cohort–MIMIC-IV database

	All patients (n = 35,845)	Alive at discharge (n = 32,524)	Death at hospital (n = 3,321)	P
Age at ICU admission, years, mean ± SD	65.0 ± 16.9	64.3 ± 16.9	70.9 ± 15.3	< 0.001
Male sex, n (%)	20,197 (56.3)	18,466 (56.8)	1,731 (52.1)	< 0.001
Body weight, kg, median [IQR]	79 [66–93]	79 [66–94]	75 [62–89]	< 0.001
Baseline sCr, mg/dL, median [IQR]	0.9 [0.7–1.2]	0.9 [0.7–1.2]	1.1 [0.8–1.6]	< 0.001
Baseline eGFR, mL/mn/1.72m^2, mean ± SD	79.2 ± 29.2	80.6 ± 28.6	65.2 ± 21.1	< 0.001
Charlson comorbidity index, median [IQR]	4 [2–5]	3 [2–5]	5 [4–7]	< 0.001
Previous conditions, n (%)				0.68
Diabetes mellitus	9,759 (27.2)	8,865 (27.3)	894 (26.9)	< 0.001
Chronic heart failure	8,547 (23.8)	7,497 (23.1)	1,050 (31.6)	< 0.001
Ischemic heart disease	5,908 (16.5)	5,234 (16.1)	674 (20.3)	< 0.001
Chronic kidney disease	5,408 (15.1)	4,709 (14.5)	699 (21.0)	< 0.001
Liver disease	3,794 (10.6)	3,085 (9.5)	709 (21.3)	< 0.001
COPD	8,498 (23.7)	7,608 (23.4)	890 (26.8)	< 0.001
ICU admission Type, n (%)				< 0.001
Cardiovascular surgery	7,670 (21.4)	7,515 (23.1)	155 (4.7)	
Medical	5,960 (16.6)	5,156 (15.9)	804 (24.2)	
Other Surgeries	5,449 (15.2)	4,881 (15.0)	568 (17.1)	
Trauma	4,524 (12.6)	4,104 (12.6)	420 (12.6)	
Non-surgical cardiopathies	4,007 (11.2)	3,576 (11.0)	431 (13.0)	
Neurologic events	2,678 (7.5)	2,478 (7.5)	200 (6.0)	
Not classified	5,557 (15.5)	4,814 (14.8)	743 (22.4)	
Higher nonrenal SOFA, median [IQR]	4 [2–6]	3 [2–6]	7 [5–10]	< 0.001
Need of mechanical ventilation, n(%)	27,984 (78.1)	25,164 (77.4)	2,820 (84.9)	< 0.001
Need of vasoactive drugs, n(%)	13,242 (36.9)	11,212 (34.5)	2,030 (61.1)	< 0.001
Need of KRT, n(%)	908 (2.5)	498 (1.5)	410 (12.3)	< 0.001
ICU LOS, days, median [IQR]	2.2 [1.5–4.1]	2.2 [1.4–3.9]	3.8 [2.0–7.4]	< 0.001

ICU intensive care unit, *kg* kilogram, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *SOFA* Sequential Organ Failure Assessment, *KRT* kidney replacement therapy, *LOS* length of stay

SOFA score during the ICU stay was 4 [IQR, 2–6], and the median LOS in the ICU was 2.2 [1.5–4.1] days. The hospital mortality rate was 9.3%. Most patients (n = 29,109; 81.2%) used an indwelling urinary catheter, and 2.7% (n = 942) used another device for urine collection during their ICU stay. Moreover, 91.9% of all UO measurement recordings were from a urinary device. The demographic and clinical characteristics of the patients in the validation cohort (eICU database) are shown in Additional file 1: Table S1.

Urine output as a predictor of hospital mortality

We evaluated the ability of the lowest urine output (UO) to predict hospital mortality using time frames of 3, 6, 12, and 24 h. All time frames demonstrated good discriminatory capacity except for the 24-h time frame. The area under the receiver operating characteristic curve (AUC-ROC) values were 0.75 [0.74–0.76], 0.75 [0.74–0.76], 0.73 [0.72–0.74], and 0.69 [0.68–0.70] for the 3-h, 6-h, 12-h, and 24-h time frames, respectively.

Defining categorical UO classification according to the time frame to compose a unified proposed UO-AKI classification

After constructing AUC-ROC curves for each UO time frame, we selected three cutoff points from each time frame using the Youden index. The AUC–ROC curves comparing UO as a continuous variable or as a categorical variable for each time frame were very similar, with minimal loss of discriminatory capacity (see Additional file 2: Table S2).

We compared the Youden index of each time frame according to the UO cutoff stage. As shown in Table 2, the 6-h time window had the best combined sensitivity and specificity across all stages. Notably, the Youden indices for Stages 2 and 3 were similar for the 3-h and 6-h time frames. For simplicity (as stage 1 for the 6-h

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Table 2 Sensitivity, specificity, and Youden index of selected cutoff points according to stage severity for each time frame

UO Proposed Stage	UO threshold (mL/kg/h)	Sensitivity	Specificity	Youden Index
3 h Time Frame				
Stage 1	0.36	93%	26%	0.19
Stage 2	0.11	62%	77%	0.40
Stage 3	0.05	40%	91%	0.33
6 h Time Frame				
Stage 1	0.30	80%	54%	0.34
Stage 2	0.20	65%	74%	0.40
Stage 3	0.10	42%	91%	0.33
12 h Time Frame				
Stage 1	0.60	86%	37%	0.23
Stage 2	0.30	61%	75%	0.36
Stage 3	0.15	36%	92%	0.27
24 h Time Frame				
Stage 1	1.00	89%	28%	0.18
Stage 2	0.46	62%	70%	0.32
Stage 3	0.30	43%	83%	0.26

UO: urine output

time frame had a better Youden index than other time frames) and because a 6-h time window is the most practical in the daily practice of most ICUs, we chose the 6-h time frame values to compose our proposed UO-AKI classification: Stage 1: 0.2–0.3 mL/kg/h; Stage 2: 0.1–0.2 mL/kg/h; and Stage 3: < 0.1 mL/kg/h over 6 h. According to this classification, the incidence of UO-AKI was 49.0%, and the great majority of these patients (89.8%) had UO measured by any device. The distribution of patients according to the proposed UO-AKI stage is shown in Additional file 3: Table S3–average method.

Average or persistent UO reduction

Before comparing our proposed UO-AKI classification with the current KDIGO classification, we evaluated whether a classification based on persistently reduced hourly UO over consecutive 6 h is superior to the average method using the same UO thresholds. As expected, the persistent method resulted in a lower diagnosis rate of UO-AKI at each stage than did the average method (see Additional file 3: Table S3). However, the average method demonstrated better discriminatory capacity than the persistent method (AUC-ROC 0.74, 95% CI 0.73–0.75 vs. 0.70, 95% CI 0.69–0.71; see Additional file 8: Fig. S1). From this point onward, the proposed UO-AKI classification utilizes the average method within a 6-h time frame.

The proposed UO-AKI classification is independently associated with increased hospital mortality in a stepwise pattern

According to the univariate analysis, the proposed UO-AKI classification was associated with in-hospital mortality, showing a stepwise increase in the odds ratio with advancing UO-AKI stage (see Additional file 4: Table S4). After adjusting for age, sex, baseline serum creatinine (sCr) level, Charlson Comorbidity Index, ICU admission type, worst nonrenal SOFA score, and the need for KRT, the associations remained significant, with a stepwise increase in the odds ratio (Fig. 2).

Proposed UO-AKI classification vs. KDIGO UO-AKI classification

Compared to the KDIGO UO-AKI criteria, the proposed UO-AKI criteria demonstrated a greater discriminatory capacity for predicting hospital mortality (Fig. 3a). Additionally, we evaluated the different UO-AKI staging criteria using the NRI. The proposed UO-AKI criteria showed a total NRI of 26.4% (95% CI: 24.5–28.9) compared to the KDIGO UO-AKI criteria (see Table 3). Furthermore, 4.1% (95% CI: 3.7–4.6) of patients were positive for IDI, indicating that the proposed UO-AKI classification was superior.

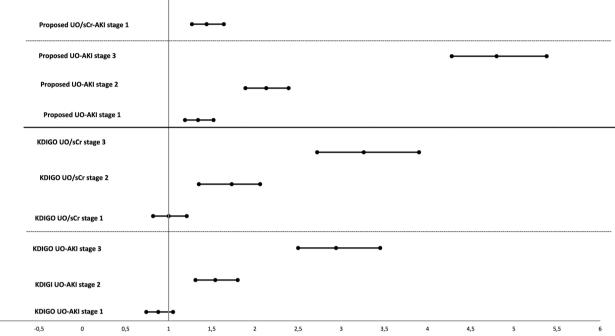Machado *et al. Critical Care*   (2024) 28:272

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Fig. 2 Adjusted odds ratio for hospital mortality per acute kidney injury (AKI) severity stage according to proposed and Kidney Disease: Improving Global Outcomes (KDIGO) urinary output (UO) or UO/serum creatinine (sCr) criteria. The association between AKI severity and in-hospital mortality was explored with a multivariate logistic regression model. The variables included in the model were age, sex, baseline serum creatinine (sCr) level, Charlson Comorbidity Index, type of ICU admission, worst nonrenal SOFA score, and the need for KRT

sCr criteria combined with the proposed UO-AKI classification

We utilized the proposed UO stages to establish a UO/sCr-AKI classification, employing the same sCr increment cutoffs recommended by KDIGO. Table 4 compares these proposed criteria with the complete KDIGO criteria. While we observed a stepwise increase in the odds ratio with advancing UO/sCr-AKI classification, KDIGO UO/sCR-AKI stage 1 did not show an independent association with hospital mortality (Fig. 2). Compared with the KDIGO UO/sCr-AKI criteria, the proposed UO/sCr-AKI criteria demonstrated superior discriminatory capacity for predicting hospital mortality (Fig. 3b). Additionally, the proposed classification showed a positive NRI of 25.4% (95% CI: 23.3–27.6) and an IDI of 4.0% (95% CI: 3.6–4.5). Additional file 5: Table S5 displays patients according to UO or sCr criteria according to the proposed AKI criteria. The agreement between both UO and sCr was 50.2%.

Kidney-centered outcomes

We compared the proposed UO or UO/sCr-AKI criteria against the corresponding KDIGO criteria with respect to kidney-centered outcomes. The UO-AKI criteria were used to assess performance in predicting progression to stage 2/3 sCr-AKI (excluding the need for KRT) and stage 3 sCr-AKI, including KRT. Additionally, the proposed UO/sCr-AKI criteria and the KDIGO criteria were compared regarding the need for isolated KRT. Table 5 presents the AUC-ROC, NRI, and IDI for each outcome. In all comparisons, the proposed criteria outperformed the KDIGO criteria.

Additional analysis

We performed a sensitivity analysis based on the use of loop diuretics during the study period and baseline renal function (eGFR < 60 ml/min/1.73 m^2 or > 60 ml/min/1.73 m^2). The AUC-ROC, NRI, and IDI values are shown in Additional file 6: Table S6. According to all

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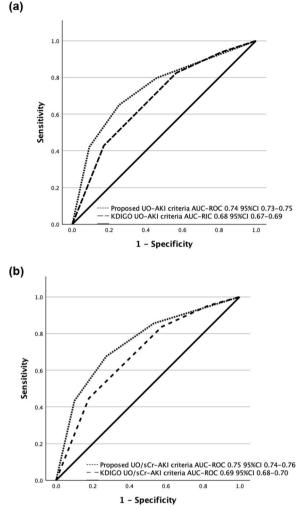
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(a)

(b)

Fig. 3 Area under the curve-receiver operating characteristic (AUC-ROC) curve for the **a** Proposed and KDIGO UO-AKI criteria and **b** Proposed and KDIGO UO/sCr-AKI criteria. The AUC-ROC curve was used to predict hospital mortality in the developing (MIMIC-IV database) cohort

sensitivity analyses, the proposed UO/sCr-AKI classification was superior to the KDIGO classification.

Additionally, we performed a Cox regression analysis, adjusting for age, sex, baseline serum creatinine (sCr) level, Charlson Comorbidity Index, ICU admission type, worst nonrenal SOFA score, and the need for KRT, to evaluate the association of both criteria with 90-day mortality. There was separation among the four groups according to the proposed UO/sCr-AKI criteria; however, according to the KDIGO UO/sCr-AKI criteria, patients with no AKI and those with stage 1 AKI were not significantly different (P = 0.60) (see Additional file 9: Fig. S2a and S2b).

External validation

The eICU database (n = 72,141) was utilized to externally validate the proposed UO/sCr-AKI classifications. According to the univariate analysis, after adjusting for age, sex, baseline eGFR, comorbidities, ICU severity score (APACHE-IV), and type of ICU admission, there was a significant stepwise increase in the OR for hospital mortality according to the proposed UO-AKI classification (see Additional file 7: Table S7). The proposed criteria showed a progressive increase in OR across all AKI stages, a pattern not observed with the KDIGO criteria. Additionally, the proposed classification system demonstrated a superior AUC-ROC curve (0.70, 95% CI 0.69–0.70 vs. 0.62, 95% CI 0.61–0.63; Fig. 4). The NRI was 17.2% (95% CI 15.5–18.8), and the IDI was 3.1% (95% CI 2.7–3.5).

Discussion

In this study, we explored hourly UO in different time frames to select stricter UO thresholds for developing a novel UO-based classification system for AKI in critically ill patients. Our findings indicate that this simple (all thresholds selected were from a 6 h time frame) new classification system has superior predictive value for hospital mortality compared to the current KDIGO UO-AKI criteria. Additionally, the combined UO/sCr-AKI classification system (with current KDIGO sCr increments) showed improved predictive accuracy and patient stratification. Finally, we validated our proposed UO/sCr-AKI criteria using a large independent population.

In recent years, researchers have suggested that UO-AKI stage 1 (< 0.5 ml/kh/h) is not independently associated with poor outcomes because it is too liberal [5, 18]. Our data agree with other studies that failed to demonstrate an independent association between UO or UO/sCr KDIGO stage 1 AKI and outcomes [3, 6, 16]. Additionally, several studies support our findings that a UO of 0.3 mL/kg/h is a better cutoff where reduced UO begins to be associated with main outcomes [5, 7, 9]. In fact, our analysis revealed that the UO threshold with the best sensitivity and specificity in a 6 h window was 0.2 ml/kg/h. This value is the same as that recently described by Bianchi et al. [6] in a large cohort of critically ill patients. However, to construct a staging system with four stages, a stepwise reduction in sensitivity and an increase in specificity with increasing severity are expected and desirable; although a threshold of 0.2 ml/kg/h had the best accuracy, it had intermediate sensitivity and specificity compared with other thresholds defining stages 1 and 3 (0.3 and 0.1 ml/kg/h, respectively).

As stated in the introduction, the ideal definition of oliguria involves various aspects. This study focused on

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one aspect: the impact on short-term clinical outcomes and 90-day mortality. Even if not classified as AKI by the proposed criteria, some patients with higher UO thresholds can accumulate waste solutes and/or present elevated renal biomarkers, indicating structural damage. Whether this degree of renal injury can lead to long-term consequences, such as progressive loss of renal function, requires further study. In this way, if new therapies that impact the progression of AKI are developed and prove effective in very early stages, the definition may be reformulated to encompass earlier stages based on both UO and other biomarkers.

One strength of our study is that we evaluated the lowest UO in several time frames as a continuous variable. This approach not only sought to identify the threshold with an independent association with the outcome but also aimed to determine the thresholds with the best discrimination from each time frame and construct a unique proposed classification. As shown in Table 2, the thresholds for stages 2 and 3 in the 3-h and 6-h time frames had similar Youden indices. However,

we preferred to develop our classification system using a 6-h window because stage 1 from the 6-h time frame had a better Youden index than did the other time windows; we believe this is more common in daily practice, and a previous study demonstrated that 3–5 h of consecutive reduced UO is a valuable measure of AKI risk [19]. Nevertheless, our findings suggest that a 3-h time frame could be used as an early warning signal.

Another discussion in the literature is how to apply the UO threshold in mL/kg/h to diagnosis and stratify AKI patients. Basically, we have 3 methods: average UO in a time frame with fixed blocks, average UO with sliding windows hourly (or up next UO register) or persistent UO less than the cutoff each hour within a time frame [20]. Recently, Monard et al. [10] demonstrated a significant difference in AKI diagnosis when using average versus persistent UO methods. In our study, we developed our proposed classification system using the average UO with a sliding window. However, we compared our method with the persistent method and revealed that the average method exhibited

Table 3 Acute kidney injury incidence using the proposed and KDIGO criteria based on urine output (UO) only (table a) and UO/serum creatinine (sCr)—AKI criteria (table b) and net reclassification according to hospital mortality. Gray indicates patients who were correctly reclassified and blue those who were incorrectly reclassified

		KDIGO UO-AKI Criteria			
		Hospital mortality: yes			
		No-AKI	AKI stage 1	AKI stage 2	AKI stage 3
Proposed UO-AKI criteria	**No-AKI**	205	217	167	84
	AKI stage 1	-	89	352	48
	AKI stage 2	-	48	476	238
	AKI stage 3	-	22	322	1,053
		Hospital mortality: no			
		No-AKI	AKI stage 1	AKI stage 2	AKI stage 3
	No-AKI	6,104	5,472	3,952	2,067
	AKI stage 1	-	1,720	4,292	639
	AKI stage 2	-	623	3,496	1,161
	AKI stage 3	-	186	1,098	1,714

Urine Output Criteria Only		
Proportion reclassified up correctly: positive composite outcome	11.8%	NRI (95%CI) favoring proposed classification: 26.4% (24.5-28.9)
Proportion reclassified down incorrectly: positive composite outcome	33.3%	
Proportion reclassified up incorrectly: negative composite outcome	5.9%	
Proportion reclassified down correctly: negative composite outcome	54.1%	

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Table 3 (continued)

Proposed UO/sCr-AKI criteria	KDIGO UO/sCr-AKI Criteria			
	Hospital mortality: yes			
	No-AKI	**AKI stage 1**	**AKI stage 2**	**AKI stage 3**
No-AKI	157	153	114	55
AKI stage 1	-	172	358	68
AKI stage 2	-	45	525	234
AKI stage 3	-	15	297	1,128
	Hospital mortality: no			
	No-AKI	**AKI stage 1**	**AKI stage 2**	**AKI stage 3**
No-AKI	5,537	4,514	3,270	1,875
AKI stage 1	-	2,989	4,670	776
AKI stage 2	-	593	3,876	1,164
AKI stage 3	-	176	1,085	1,990

Combined Urine Output and Serum Creatinine Criteria		
Proportion reclassified up correctly: positive composite outcome	10.7%	NRI (95%CI) favoring evaluated classification: 25.4% (23.3-27.6)
Proportion reclassified down incorrectly: positive composite outcome	29.6%	
Proportion reclassified up incorrectly: negative composite outcome	5.7%	
Proportion reclassified down correctly: negative composite outcome	50.0	

Table 4 Proposed and Kidney Disease Improving Global Outcomes (KDIGO) classification for acute kidney injury (AKI)

Stage	KDIGO AKI Classification	Proposed AKI Classification
1	Urine < 0.5 ml/kg per hour for 6 h; sCr = 0.3-mg/dl rise within 48 h or ≥ 1.5 × −1.9 × baseline	Average urine < 0.3 ml/kg per hour for 6 h; sCr = 0.3-mg/dl rise within 48 h or ≥ 1.5 × −1.9 × baseline
2	Urine < 0.5 ml/kg per hour for 12 h; sCr ≥ 2.0 × −2.9 × baseline	Average urine < 0.2 ml/kg per hour for 6 h; sCr ≥ 2.0 × −2.9 × baseline
3	Urine < 0.3 ml/kg per hour for 24 h; sCr ≥ 3 × baseline or sCr ≥ 4 mg/dL	Average urine < 0.1 ml/kg per hour for 6 h; sCr ≥ 3 × baseline or sCr ≥ 4 mg/dL

better discriminatory capacity in predicting hospital mortality.

In daily adult ICUs, daily sCr measurements are nearly as accessible as those of UOs. It would be less valuable if reclassifying AKI staging based on UO did not contribute additional discriminatory information and risk reclassification for each patient. Our study advances in this regard, as it is the first, to the best of our knowledge, to assess the added significance of a new UO threshold for AKI staging based on sCr. According to both the proposed and KDIGO criteria, the UO and UO/sCr-AKI criteria demonstrated similar discriminatory capacities. Our findings align with a previous Canadian study [21], which showed a slight improvement in the AUC-ROC when the sCr criteria were added to the UO criteria (0.03 and 0.02 in univariate and multivariate analyses, respectively). Although the discrimination values were comparable, the agreement between the proposed UO and sCr-AKI criteria was approximately 50% (Additional file 5: Table S5), suggesting that the UO and sCr criteria identify different patients.

Another critical point to highlight is the external validation of our proposed UO/sCr-AKI classification in a large cohort U.S. multicenter database. Although it is anticipated that the performance of any model may diminish in a validation cohort compared to that in a

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Table 5 Area under the receiver operating characteristic curve (AUC-ROC), net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for both criteria for kidney-centered outcomes

	Outcome: Progression to sCr-AKI stage 2/3 (without KRT)		
	AUC-ROC	NRI	IDI
Proposed UO AKI-criteria	0.75 (0.73–0.76)	27.9 (25.3–30.5)	3.9 (3.4–4.4)
KDIGO UO AKI-criteria	0.68 (0.67–0.70)		
	Outcome: Progression to sCr-AKI stage 3 (including KRT)		
	AUC-ROC	NRI	IDI
Proposed UO AKI-criteria	0.80 (0.79–0.82)	29.5 (25.3–33.5)	2.8 (2.4–3.1)
KDIGO UO AKI-criteria	0.75 (0.74–0.77)		
	Outcome: Need of KRT		
	AUC-ROC	NRI	IDI
Proposed UO/sCr AKI-criteria	0.85 (0.83–0.86)	33.2 (30.1–36.3)	2.6 (1.9–3.3)
KDIGO UO/sCr AKI-criteria	0.81 (0.79–0.82)		

development cohort [22], the KDIGO criteria showed, at best, modest discriminatory capacity in our validation cohort. This discrepancy can be partly attributed to differences in the granularity of UO data between the MIMIC-IV and eICU databases. In the MIMIC-IV, UO values are typically recorded hourly for most patients, whereas in the eICU database, intervals are longer and potentially less precise. For instance, the median number of urine output entries per 24-h ICU LOS was almost four times greater in the MIMIC-IV database than in the eICU database. Despite these differences, disparities
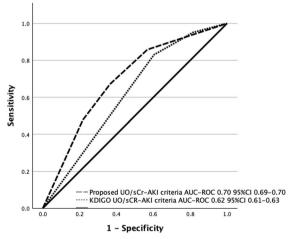

Fig. 4 Area under the curve-receiver operating characteristic (AUC-ROC) curve for the proposed and KDIGO UO/sCR-AKI criteria. The AUC-ROC curve was used to predict in-hospital mortality in the validation (eICU database) cohort

in discrimination and reclassification between our proposed criteria and the KDIGO criteria persisted.

This study has several limitations, beyond those related to all the aspects that the definition of oliguria should ideally address, that should be considered. First, the retrospective nature of the analysis may introduce biases related to data collection and patient selection. Despite the use of robust databases, there are differences in the disponible variables (for example, severity scores in the ICU) and the granularity of the data, potentially affecting the accuracy of AKI classification. Mainly, UO measurements in the MIMIC-IV and eICU databases are made by bedside nurses, and a recent study suggested that electronic UO monitoring is significantly more accurate than manual measurement [23]. Although not available in the majority of ICUs, future studies are necessary to determine the impact of electronic UO monitoring on AKI classification. Additionally, the exclusion of patients with missing baseline serum creatinine (sCr) and those lacking weight records may limit the generalizability of our findings. The reliance on a 6-h UO threshold, while practical, may not capture the full spectrum of AKI severity, and further studies are needed to validate these findings across diverse patient populations and clinical settings, for example, in noncritically ill patients.

In conclusion, this study leveraged UO as a continuous variable over various time intervals to identify the best UO thresholds and advanced beyond mere associations with mortality by demonstrating superior discriminative capacity and reclassification potential. We propose a novel UO-AKI classification system. This proposed classification proved to be simpler,

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relying solely on a 6-h interval, and superior to the current KDIGO criteria. Furthermore, this classification remained superior even when the sCr criterion was included and was externally validated in an independent population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05054-3.

Additional file 1. Table S1: Patient demographics and characteristics at the first 28 days of ICU stay or up to kidney replacement therapy initiation from the validation cohort – eICU database.

Additional file 2. Table S2: Discriminatory capacity of the lowest urine output as a continuous or categorical variable according to time frame. Cutoff points were selected based on the Youden index.

Additional file 3. Table S3: Acute kidney injury stages by proposed urine output thresholds according to average or persistent reduced urine output.UO: urine output.

Additional file 4. Table S4: Odds ratio for the proposed UO-AKI classification for in-hospital mortality according to univariate analysis.

Additional file 5. Table S5: Patients distribution according to urine output or serum creatinine criteria according to the proposed acute kidney injury criteria.

Additional file 6. Table S6: Discrimination difference, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) from comparisons between the proposed and KDIGO UO/sCr-AKI criteria.

Additional file 7. Table S7: Unadjusted and adjusted odds ratios for each AKI stage for the proposed and KDIGO UO/sCr criteria in the validation cohort (eICU database).

Additional file 8. Figure S1: Discrimination capacity of the proposed UO-AKI classification system using the average and persistent reduced urine output methods.

Additional file 9. Figure S2: Adjusted 90-day survival rates according to AKI severity according to the KDIGO (a) and proposed (b) criteria. Adjusted for age, sex, type of ICU admission, Charlson comorbidity index, nonrenal SOFA score and need for kidney replacement therapy during the ICU stay.

Declarations

Ethics approval and consent to participate
The MIMIC-IV and eICU databases are publicly available, and researchers who agree to the data use agreement and have completed "protecting human subjects training" can request access. The MIMIC database was approved by the institutional review boards of the Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (No. 0403000206), which waived the requirement for individual patient consent because the datasets contained deidentified information. Ethics approval of the eICU database was not applicable because it was released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision (HIPAA Certification No. 1031219-2).

Competing interests
The authors declare no competing interests.

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