Choice of Reference Creatinine for Post-Traumatic Acute Kidney Injury Diagnosis

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BACKGROUND: Acute kidney injury (AKI) after trauma is associated with poor outcomes. According to current guidelines, a diagnosis of AKI should be made based on an increase in serum creatinine from a reference value. However, a true reference is often unknown in patients presenting with traumatic injury. The aim of this study was to determine the optimal reference creatinine estimate for post-traumatic AKI diagnosis and staging. The optimal reference estimate was defined by a high incidence, strong prognostic ability, and incrementality at each stage.

STUDY DESIGN: This was a cohort study of adult trauma patients (older than 16 years) requiring ICU admission between 2009 and 2018 (n = 8,026) at a single Level I trauma center. AKI was determined using the following 4 reference creatinine estimates: Modified Diet of Renal Diseases (MDRD), Trauma MDRD, admission creatinine, and the first-day creatinine nadir. Inclusivity was assessed by incidence of AKI diagnosed with different reference creatinine estimates; prognostic ability was assessed by multivariable modified Poisson regression; and incrementality was assessed by correlation of mortality risk by AKI stage.

RESULTS: There was a wide range of AKI incidence, from 21% when using admission creatinine to 76% using the Trauma MDRD. The MDRD reference creatinine estimate resulted in an AKI incidence of 41% and a diagnosis that was both prognostic of mortality and incremental with each AKI stage. All other reference estimates resulted in AKI diagnoses that were either not prognostic or not incremental.

CONCLUSIONS: Reference creatinine estimate determines the clinical importance of AKI diagnoses. In this study, the MDRD reference resulted in optimal AKI diagnoses. (J Am Coll Surg 2019; 229:580–588. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Acute kidney injury (AKI) after trauma is associated with increased mortality and cost and prolonged length of stay.[1-3] Acute kidney injury encompasses a spectrum of kidney dysfunction from asymptomatic renal insufficiency to severe AKI requiring dialysis. The reported incidence of post-traumatic AKI ranges from 1% to 55%.[4-7] This wide variation has been attributed to changing and ambiguous clinical definitions of AKI, which has been perpetuated by a lack of a clinically available gold standard for AKI diagnosis.[8]

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Abbreviations and Acronyms

AKI = acute kidney injury
GFR = glomerular filtration rate
MDRD = Modified Diet of Renal Diseases
TMDRD = Trauma Modified Diet of Renal Diseases
KDIGO = Kidney Disease Improving Global Outcomes
TQIP = Trauma Quality Improvement Program

The diagnostic criteria of AKI have evolved during the past few decades. Most recently, the Kidney Disease Improving Global Outcomes (KDIGO) group released recommendations for creatinine-based AKI diagnosis.[9] These criteria are based on an increase from a baseline, or reference, creatinine. Acute kidney injury is staged on the degree of increase from the reference creatinine. However, trauma patients frequently present without a reference creatinine, resulting in inconsistent AKI diagnoses. There are no current guidelines recommending how to estimate reference creatinine.

To improve the diagnostic criteria of post-traumatic AKI, an optimal reference creatinine should be established. According to the Guidelines International Network Preventing Overdiagnosis Working Group, the resulting AKI definition should be inclusive, capturing as many patients as possible who might benefit from treatment, and excluding the patients who might be harmed from treatment; prognostic, or predicting clinically meaningful outcomes; and incremental, providing clinically meaningful information at each stage.[10]

The objective of this study was to establish the reference creatinine estimate resulting in an optimal post-traumatic AKI diagnosis based on incidence, prognosis, and incrementality by AKI stage. The hypothesis evaluated in this study was that there would be significant variation in the strength of association between AKI diagnosis and clinical outcomes, such as mortality, based on the reference creatinine used.

METHODS

A retrospective cohort study was conducted at Memorial Hermann Hospital Texas Medical Center, a high-volume, Level I trauma center in Houston, TX. Adult (16 years and older) trauma patients requiring ICU admission during a 10-year period from 2009 to 2018 were included. Patients with pre-existing end-stage renal disease or those admitted to the burns service were excluded. STROBE (Strengthening of the Reporting of Observational Studies in Epidemiology) guidelines for observational studies were followed.[11] The McGovern Medical School at UTHealth IRB approved this study. Demographic characteristics, medical history, injury details, and secondary outcomes of in-hospital mortality, hospital-free days, and ICU-free days were obtained from the institution's prospectively maintained trauma registry. Laboratory results were extracted from the medical record.

Four methods for estimating reference serum creatinine were identified in the trauma literature: Modified Diet of Renal Diseases (MDRD), Trauma-MDRD (TMDRD), admission creatinine, and first-day creatinine nadir.

The MDRD uses race, age, and sex to estimate a reference creatinine.[5,7,12] The version used in trauma literature and in this study was calibrated to an assumed creatinine clearance of 75 mL/min, as recommended by international guidelines.[13] The trauma-specific MDRD is a similar equation that was designed to estimate creatinine for the young and generally healthy trauma population, but uses the highest median glomerular filtration rate (GFR) demonstrated by trauma patients during the first week of admission in an earlier study, which was found to be 121 mL/min[2,4,14,15] (eFig. 1). Admission creatinine was defined as the first serum creatinine measurement after hospital arrival,[2] and the first-day nadir was defined as the lowest creatinine measured within 24 hours of arrival.[4]

Outcomes measures

This study assessed the following 3 primary outcomes: inclusivity, prognostic ability, and incrementality. Inclusivity was assessed using AKI incidence. Prognostic ability

was assessed using the estimated relative risk of mortality with AKI diagnosis. Finally, incrementality was assessed by evaluating whether there was a stepwise increase in mortality by AKI stage. AKI diagnosis was made based on the current guidelines published by the KDIGO group.[9] The highest creatinine within 1 week of admission was compared with the assigned reference creatinine estimate to determine the increase from baseline. A patient was diagnosed with AKI and given a stage, if indicated. AKI was diagnosed if there was an increase in serum creatinine of $\geq$0.3 mg/dL within 48 hours or an increase in serum creatinine to $\geq$1.5 times reference within 7 days. A patient was assigned to stage 1 if their serum creatinine increased 1.5 times reference up to 2.0 times reference. Stage 2 was assigned if their serum creatinine increased from 2.0 up to 3.0 times the reference. Finally, stage 3 was assigned if their serum creatinine increased $\geq$3.0 times the reference or was >4.0 mg/dL. Stage 3 was also assigned if the patient required renal replacement therapy. The KDIGO guidelines include urine output criteria, but these were not considered in this study due to inability to verify accuracy of available data. AKI incidence was defined as the proportion of patients with AKI among total included patients. Other outcomes were obtained from the trauma registry: in-hospital mortality, 30-day ICU-free days, and 30-day hospital-free days.

Statistical analysis

Statistical analyses were conducted using R, version 3.53 (R Foundation for Statistical Computing). Incidence, demographics, and outcomes were compared between no-AKI and AKI groups for each reference estimate. Continuous variables were presented as medians (interquartile range). Chi-square and Wilcoxon rank-sum tests were used to compare categorical and continuous demographic data and secondary outcomes, respectively, between no-AKI and AKI groups. Additionally, secondary outcomes were assessed by AKI stage. A kappa statistic was calculated for AKI diagnosis between each of the reference estimates.

The data set was split 66%/34% to develop and validate in-hospital mortality models for each creatinine reference estimate. Modified Poisson regression was used to estimate relative risks. This method has been proposed as an alternative to log binomial models when convergence is a problem (as was the case here).[16] Model discrimination was evaluated with area under the curve. Secondary Poisson regression models included covariates that were selected on a subsample of this cohort using univariate analyses ($p < 0.20$, data not shown). Similar models were created including each stage of AKI as an ordinal variable. Validation of each multivariable model was conducted by calculating the area under the curve on the validation sample. Spearman correlation coefficients were generated to evaluate incrementality of mortality risk with increasing AKI stage. Patients with missing data were excluded from the multivariable analyses.

Two sensitivity analyses were performed. First, to better explore the age-related spectrum of renal dysfunction highlighted by the MDRD and the TMDRD, hybrid reference estimates were generated using different reference estimates at different ages: TMDRD, used with younger age, and the MDRD, used with the older age. These were assessed similarly to the other reference estimates as described. Second, to ensure covariate selection was adequate, each analysis was repeated using a model with additional emergency department variables, including race, sex, year of care, transfer status, trauma type, and Glasgow Coma Scale.

RESULTS

There were 8,026 patients admitted to the trauma ICU during the 10-year study period. Forty-eight patients were excluded, 23 for end-stage renal disease present on admission and 25 for admission to the burns service, resulting in 7,978 patients remaining for analysis. Less than 1% of data were missing. Median age was 41 years (interquartile range 26 to 58 years). Male sex was predominant, accounting for 72% of the cohort. Participants were severely injured, with a median Injury Severity Score of 20 (interquartile range 13 to 29). Resulting reference creatinine values were lowest when using the TMDRD and highest when using the admission creatinine or MDRD equation (Table 1). On univariate analysis, patients with AKI diagnosed by any reference estimate were more severely injured and arrived with a lower systolic blood pressure. Patients with AKI diagnosed using the MDRD, TMDRD, or admission creatinine estimates were older than those without AKI. Patients with AKI diagnosed with the MDRD or TMDRD were more likely to be female than those without AKI. Across reference creatinine estimates, patients with AKI had fewer 30-day hospital-free days and a higher mortality rate than those without AKI (Table 2).

Inclusivity

The incidence of AKI during the first week of admission differed widely between reference creatinine estimates (Table 2). The incidence of AKI varied from 21% using the admission creatinine to estimate the reference creatinine to 76% using the TMDRD. Other reference estimates resulted in AKI incidences of 41% using the

Table 1. Characteristics of Study Participants

Variable	All patients (n = 7,978)
Age, y, median (IQR)	41 (26–58)
Year, n (%)	
2009	726 (9)
2010	719 (9)
2011	812 (10)
2012	915 (11)
2013	884 (11)
2014	851 (11)
2015	858 (11)
2016	816 (10)
2017	837 (10)
2018*	560 (7)
Male sex, n (%)	5,774 (72)
Race/ethnicity, n (%)	
White	4,176 (52)
Black	1,324 (17)
Hispanic	1,739 (22)
Asian	133 (2)
Blunt mechanism of injury, n (%)	6,766 (85)
Injury Severity Score, median (IQR)	20 (13–29)
Arrival systolic blood pressure, mmHg, median (IQR)	122 (101–142)
Arrival base deficit, mmol/L, median (IQR)	4 (8–1)
Baseline creatinine, mg/dL, median (IQR)	
MDRD	1.1 (1.0–1.2)
Trauma MDRD	0.7 (0.6–0.8)
Admission creatinine	1.1 (0.9–1.4)
First-day nadir	0.9 (0.7–1.2)
30-day ICU-free days, median (IQR)	26 (17–28)
30-day hospital-free days, median (IQR)	16 (4–23)
Length of stay, n (%)	
<1 wk	2,507 (31)
Discharged	1,950 (78)
Mortality	557 (22)
In-hospital mortality, n (%)	825 (10)
Mortality <1 wk	557 (68)

*Complete data through 10 months.
IQR, interquartile range; MDRD, Modified Diet of Renal Diseases.

MDRD and 54% using the first-day nadir. These diagnoses correlated poorly with each other, as assessed by the kappa inter-relater correlation coefficient, with all values <0.50 (eTable 1).

Prognosis

On univariate analysis, the MDRD, TMDRD, admission creatinine, and first-day nadir resulted in AKI diagnoses that correlated with mortality ($p \leq 0.01$). After adjusting for age, arrival systolic blood pressure, and Injury Severity Score, the direction of associations between AKI diagnoses and mortality remained unchanged (Fig. 1, eTable 2). The estimated relative risk of increased mortality revealed associations with AKI diagnosed using the MDRD, admission creatinine, and first-day nadir.

Incrementality

Mortality by AKI stage was calculated for each reference estimate (eTable 4). On multivariable regression, the MDRD resulted in AKI stages in which the associated relative risk of mortality incrementally increased with increasing AKI stage (Fig. 2). Estimated relative risk of mortality by AKI stage using the MDRD reference estimate resulted in a positive Spearman's correlation coefficient (ρ) = 1 ($p < 0.001$). Acute kidney injury stage did not correlate with estimated relative risk of mortality when using the remainder of the reference estimates for AKI staging: TMDRD $\rho = 0.5$ ($p = 0.67$), admission creatinine $\rho = 0.5$ ($p = 0.67$), and first-day nadir $\rho = 0.5$ ($p = 0.67$).

Model validation

Each of the models created to assess the relationship between AKI or AKI stage and mortality was applied to the test cohort. Area under the curves for the models ranged from 0.78 to 0.80 (eTable 3).

Sensitivity analyses

Hybrid AKI diagnoses were generated using different ages to transition from using the TMDRD to the MDRD reference estimates. Crossover occurred from 25 to 60 years of age at 5-year increments. Prognosis and incrementality were assessed according to the procedures mentioned (eFig. 2). The hybrid reference estimates were associated with mortality when the transition from TMDRD to MDRD occurred at age 50 years or younger. Estimated relative risk of mortality by AKI stage using all hybrid reference estimates was incremental, with a $\rho = 1$ ($p < 0.001$). The second sensitivity analysis using a full model for the multivariable analyses resulted in similar findings as the model with fewer covariates.

Diagnostic criteria

The MDRD, admission creatinine, and first-day nadir reference creatinine estimates resulted in AKI diagnoses that were prognostic of mortality, and the MDRD was the only reference estimate resulting in AKI diagnoses that were incrementally associated with increasing risk of mortality (Table 3).

Table 2. Characteristics of Patients With and Without Acute Kidney Injury, by Reference Creatinine Estimate

	MDRD			Trauma MDRD			Admission creatinine			First-day nadir		
Variable	No AKI (n = 4,684 [59%])	AKI (n = 3,294 [41%])	p Value	No AKI (n = 1,916 [24%])	AKI (n = 6,062 [76%])	p Value	No AKI (n = 6,284 [79%])	AKI (n = 1,694 [21%])	p Value	No AKI (n = 3,624 [46%])	AKI (n = 4,379 [54%])	p Value
Age, y, median (IQR)	36 (24–54)	48 (31–64)	<0.001	32 (22–48)	44 (29-61)	0.001	40 (26–57)	44 (28–61)	<0.001	41 (26–58)	41 (27–58)	0.67
Male sex, %	79	63	<0.001	82	69	<0.001	72	72	1.0	72	73	0.40
ISS, median (IQR)	19 (12–29)	21 (13–29)	<0.001	19 (12–29)	20 (13-29)	0.002	20 (12–29)	22 (13–29)	0.001	19 (12–29)	21 (13–29)	<0.001
SBP, mmHg, median (IQR)	124 (105–142)	121 (98–141)	<0.001	125 (106–142)	122 (100-142)	<0.001	123 (102–142)	120 (98–141)	0.007	124 (104–143)	120 (100–140)	<0.001
Hospital-free days, median (IQR)	18 (7–24)	15 (0–22)	<0.001	18 (8–24)	16 (2-23)	<0.001	17 (6–24)	13 (0–22)	<0.001	17 (6–24)	16 (1–23)	<0.001
Mortality, %	8	13	<0.001	7	11	<0.001	9	16	<0.001	10	11	0.01

AKI, acute kidney injury; IQR, interquartile range; ISS, Injury Severity Score; MDRD, Modified Diet of Renal Diseases; SBP, arrival systolic blood pressure.

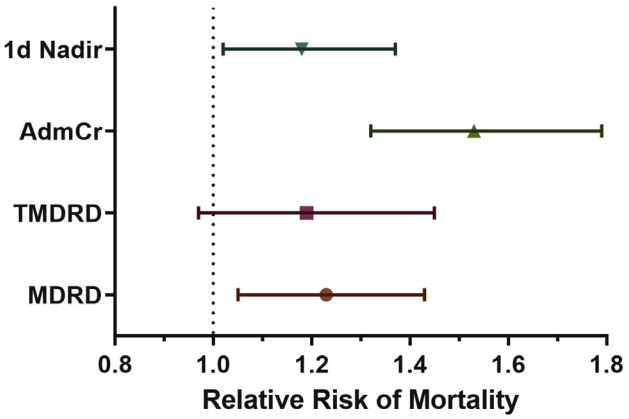

Figure 1. Estimated relative risk of mortality by acute kidney injury diagnosis, adjusted for age, arrival systolic blood pressure, and Injury Severity Score. AdmCr, admission creatinine; MDRD, Modified Diet of Renal Diseases; TMDRD, Trauma Modified Diet of Renal Diseases.

DISCUSSION

In this large cohort of severely injured trauma patients and the first report of reference creatinine estimate comparison for post-traumatic AKI, there was significant variation in the strength of association between AKI diagnosis and mortality based on the reference creatinine value used. These findings were consistent with the hypothesis. Of the pre-existing reference estimates evaluated, the MDRD reference creatinine estimate satisfied the most criteria for optimal diagnosis. The MDRD resulted in a mid-range estimate of incidence of 41%, which includes more patients than many earlier reports of post-traumatic AKI incidence.[2,6,7,15] The use of MDRD for the reference creatinine also resulted in AKI diagnosis being associated with mortality, and there was incrementality in that risk of mortality was positively correlated with AKI stage.

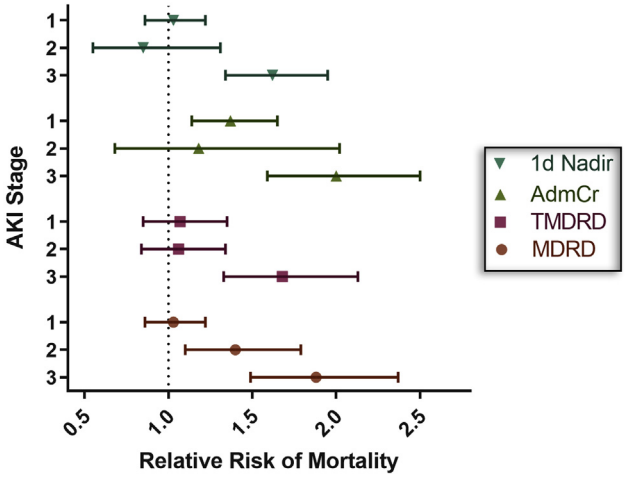

Figure 2. Estimated relative risk of mortality by acute kidney injury (AKI) stage, adjusted for age, arrival systolic blood pressure, and Injury Severity Score. MDRD, Modified Diet of Renal Diseases; TMDRD, Trauma Modified Diet of Renal Diseases.

Similar evaluations of classification criteria have been completed in the ICU setting, such as after MI and after major cardiac operation.[17-21] A high proportion of patients in these settings presented with recent outpatient creatinine values, which could be compared with an imputed or reference creatinine estimate. In these studies, the MDRD equation systematically inflated AKI incidence, and admission creatinine systematically underestimated AKI incidence. Notably, the population was older and had a higher prehospital comorbid burden compared with trauma patients, who are generally young and healthy. Findings from earlier studies cannot necessarily be translated to trauma patients, given the different populations. Verification of reference creatinine estimates was not possible in this study because <10% of patients presented with a true reference creatinine, defined as a pre-injury creatinine within the previous 1 year.[22,23] Therefore, sensitivity, specificity, and accuracy were unable to be generated.

Post-traumatic AKI is known to be associated with patient outcomes and has been added as a quality of care measure in the national Trauma Quality Improvement Program (TQIP).[2,3] The TQIP provides participating centers with periodic reports of performance and benchmarks them against other centers. The program aims to improve the quality of care by identifying best practices and raising the performance of poorly performing centers.[24] Within the TQIP database, AKI is considered a hospital event and is classified similarly to a surgical site infection, pressure ulcer, or ventilator-associated pneumonia.[25] However, the reference estimate for AKI diagnosis in TQIP is not defined. As demonstrated by the current study, choice of reference creatinine determines the disease incidence and affects the direction and strength of the relationship between an AKI diagnosis and mortality. Benchmarking hospitals against each other without a standard reference estimate likely reduces the value of AKI as a quality measure. Uninformative measures can hinder development of best practices and improvement of hospital performance. External validation that the MDRD is the best method for estimating reference creatinine is needed to standardize trauma registry reporting and benchmarking.

Continued challenges exist for diagnosing post-traumatic AKI. Ideally, obtaining GFR and filtration function should be simple and cost-effective. However, direct measurement of GFR is not practical with exogenous agents due to cost, toxicity, and measurement

Table 3. Criteria Fulfilled for Optimal Post-Traumatic Acute Kidney Injury Diagnosis

Variable	MDRD	Trauma MDRD	Admission creatinine	First-day nadir
Inclusive, %	41	76	21	54
Prognostic	Yes	No	Yes	Yes
Incremental	Yes	No	No	No

MDRD, Modified Diet of Renal Diseases.

capacity in most clinical settings.[26] The best clinically available biomarker to assess renal function is creatinine, which has significant limitations. Creatinine is a byproduct of muscle metabolism or damage that is freely filtered, consistently produced in healthy states, and not reabsorbed. However, creatinine is also secreted, and rates of secretion increase during kidney injury, which masks the degree of GFR decline. Normal creatinine values vary widely and are dependent on several factors, including age, sex, diet, and muscle mass.[27-29] For example, a gradual decline in GFR and corresponding increase in baseline creatinine is observed during healthy aging due to nephrosclerosis-related nephron loss.[27,30] Age-related changes in GFR might not be fully accounted for in the MDRD and TMDRD equations, as highlighted by one of the sensitivity analyses performed in this study. A hybrid reference estimate might result in a more informative AKI diagnosis than those currently used by trauma centers. Development and validation of a hybrid reference estimate should be explored in future studies.

Serum creatinine measured on hospital arrival after trauma is difficult to interpret. Elevated serum creatinine is frequently suspected to represent a decline in GFR, but this might not be the case if there is no baseline creatinine available with which to compare. The KDIGO Work Group recommends using a rise from a baseline creatinine in the diagnosis and staging of AKI. Multicenter epidemiologic studies of more than 500,000 subjects have been used to establish these AKI diagnostic and staging criteria.[31-35] The staging criteria were created to indicate incremental increases in-hospital mortality, renal replacement therapy, and long-term chronic kidney disease and mortality.[36,37] However, the precision of the KDIGO criteria remains limited and the definitions are likely to continue to be modified in the future. Creatinine-based definitions of renal function are inherently flawed, but until an alternative method is validated and becomes clinically available, they are likely to be the norm for the foreseeable future. Standardization of the optimal creatinine-based post-traumatic AKI definition will allow clinical investigators to evaluate potential therapies internally and between trauma centers.

Altering diagnostic criteria has significant implications for patients. Misdiagnosis results in both under- and overtreatment of patients, along with exposure to the resulting harms. Currently, most patients with post-traumatic AKI are treated with supportive measures, including minimizing nephrotoxins, treating the etiology of shock, and optimizing fluid resuscitation.[8] Patients with acute renal failure can be offered dialysis for systemic support until the kidneys recover, but dialysis does not correct the underlying pathology. It is unclear whether standardization of reference creatinine for post-traumatic AKI diagnosis will result in earlier clinical detection and initiation of treatment measures. Moreover, it is unknown whether earlier intervention will improve overall outcomes.

There were items identified by the Guidelines International Network Preventing Overdiagnosis Working Group that were not addressed in this study.[10] As mentioned previously, precision is dependent on the availability of a gold standard with which to compare a new set of diagnostic criteria. Our population had few and nonrepresentative patients with a true reference estimate, which left our evaluation without a clinical gold standard. The Working Group also recommends evaluating repeatability and reproducibility. To achieve this aim, our next steps are to validate these findings in multicenter observational cohorts.

Limitations

Although this is the first study to evaluate different diagnostic criteria of post-traumatic AKI, several limitations exist. Urine output was not considered for AKI diagnosis and staging.[2,4,15] This results in diagnostic criteria that depart from clinical practice. However, limitations noted previously in the accuracy of urine output data available in the electronic medical record persist and therefore urine output was not used in this study. The effect of this exclusion likely resulted in an underestimation of AKI incidence across reference estimates used. Addition of urine output criteria would likely disproportionately increase the incidence of AKI when defined by admission creatinine or the MDRD, which resulted in the lowest AKI incidences. The few prospective studies that have compared urine output and creatinine-based definitions of AKI have found that the predictive power of AKI diagnosis improves with the criteria combined.[38,39] Prospective

studies of AKI after trauma should incorporate hourly urine output into AKI diagnostic criteria to optimize value of the diagnosis.

Use of mortality as an indicator of prognosis is suboptimal because mortality alone does not capture a patient's post-injury health. Additional investigation into the relationship between post-traumatic AKI and other important outcomes, including functional recovery and chronic kidney disease, are warranted in follow-up studies. Additionally, prognosis and incrementality measured by mortality models can be limited by model structure. However, given similar results in other studies, it is likely that the reported results reflect the association, or lack thereof, between AKI diagnoses and mortality.[40,41] Finally, this study does not address the underlying inadequacies of using creatinine as the clinical marker for acute renal dysfunction. However, no clinically available alternative exists.

CONCLUSIONS

Of the reference estimates used currently, the MDRD reference creatinine estimate results in inclusive, prognostic, and incremental post-traumatic AKI diagnosis and staging in this large, single-center study of severely injured trauma patients. The TMDRD, admission creatinine, and first-day creatinine nadir were suboptimal as reference estimates due to resulting AKI diagnoses that were either not prognostic or not incremental. These findings warrant multicenter validation to establish a standard reference creatinine for post-traumatic AKI diagnosis.

Author Contributions

Study conception and design: Hatton, Wei, Harvin, Finkel, Wade, Kao
Acquisition of data: Hatton, Du
Analysis and interpretation of data: Hatton, Pedroza, Wei, Harvin, Finkel, Wade, Kao
Drafting of manuscript: Hatton, Pedroza, Du, Wei, Harvin, Finkel, Wade, Kao
Critical revision: Hatton, Du, Pedroza, Wei, Harvin, Finkel, Wade, Kao

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$$\text{MDRD} = 88.4 \times \{75/[(175 \times \text{age}^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black})]\}^{-0.887}$$

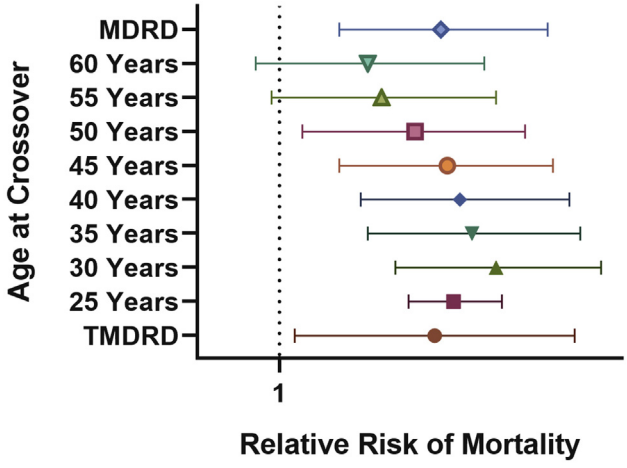
$$\text{T-MDRD} = 88.4 \times \{121/[(175 \times \text{age}^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black})]\}^{-0.887}$$

eFigure 1. Equations used for the calculation of the Modified Diet of Renal Diseases (MDRD) and Trauma MDRD (T-MDRD) reference creatinine estimates.

eTable 1. Cross-Tabulation and Kappa Coefficients Between AKI, Diagnosed with Various Reference Estimates

Variable	Cr_{adm} No AKI	Cr_{adm} AKI	Kappa
Cr_{1d} No AKI	3,617	0	0.46
Cr_{1d} AKI	2,667	1,694	
MDRD No AKI	4,398	286	0.39
MDRD AKI	1,886	1,408	
TMDRD No AKI	1,848	68	0.13
TMDRD AKI	4,436	1,626	
	Cr_{1d} No AKI	Cr_{1d} AKI	
MDRD No AKI	2,855	1,829	0.40
MDRD AKI	762	2,532	
TMDRD No AKI	1,363	553	0.27
TMDRD AKI	2,254	3,808	
	MDRD No AKI	MDRD AKI	
TMDRD No AKI	1,916	0	0.36
TMDRD AKI	2,768	3,294	

AKI, acute kidney injury; Cr_{adm}, admission creatinine; Cr_{1d}, first-day creatinine nadir; MDRD, Modified Diet of Renal Diseases; TMDRD, Trauma Modified Diet of Renal Diseases.



eFigure 2. Trauma Modified Diet of Renal Diseases (TMDRD) to Modified Diet of Renal Diseases (MDRD) crossover references relationship with mortality, adjusted for age, arrival systolic blood pressure, and Injury Severity Score.

eTable 2. Association of AKI and Mortality on Multivariable Regression, by Reference Creatinine Estimate

	MDRD			Trauma MDRD			Admission creatinine			First-day nadir		
Variable	Estimated RR	95% CI	p Value	Estimated RR	95% CI	p Value	Estimated RR	95% CI	p Value	Estimated RR	95% CI	p Value
Any AKI	1.23	1.05–1.43	0.008	1.19	0.97–1.45	0.09	1.53	1.32–1.79	<0.001	1.18	1.02–1.37	0.03
Age, y	1.02	1.02–1.03	<0.001	1.02	1.02–1.03	<0.001	1.02	1.02–1.03	<0.001	1.03	1.02–1.03	<0.001
ISS, point	1.05	1.04–1.05	<0.001	1.05	1.04–1.05	<0.001	1.05	1.04–1.05	<0.001	1.05	1.04–1.05	<0.001
Arrival SBP, mmHg	0.99	0.99–1.00	<0.001	0.99	0.99–1.00	<0.001	0.99	0.99–1.00	<0.001	0.99	0.99–0.99	<0.001

AKI, acute kidney injury; ISS, Injury Severity Score; MDRD, Modified Diet of Renal Diseases; RR, relative risk; SBP, systolic blood pressure.

eTable 3. Multivariable Model Validation, by Reference Estimate Utilized

Sample, stage	MDRD, AUC (95% CI)	Trauma MDRD, AUC (95% CI)	Admission creatinine, AUC (95% CI)	First-day nadir, AUC (95% CI)
Training (66%)				
AKI, any stage	0.79 (0.77−0.81)	0.79 (0.77−0.81)	0.79 (0.78−0.81)	0.79 (0.77−0.81)
Stage of AKI	0.79 (0.78−0.81)	0.79 (0.76−0.82)	0.80 (0.78−0.81)	0.78 (0.76−0.81)
Test (34%)				
AKI, any stage	0.79 (0.76−0.81)	0.78 (0.75−0.81)	0.79 (0.76−0.82)	0.78 (0.75−0.81)
Stage of AKI	0.80 (0.77−0.82)	0.79 (0.76−0.82)	0.80 (0.77−0.83)	0.79 (0.76−0.82)

AKI, acute kidney injury; AUC, area under the curve; MDRD, Modified Diet of Renal Diseases.

eTable 4. Mortality by AKI Stage and Reference Creatinine Estimate

	MDRD							Trauma MDRD							Admission creatinine							First-day nadir						
	Total		Survived		Died			Total		Survived		Died			Total		Survived		Died			Total		Survived		Died		
Variable	n	%	n	%	n	%	p Value	n	%	n	%	n	%	p Value	n	%	n	%	n	%	p Value	n	%	n	%	n	%	p Value
No AKI	4,684	59	4,303	91	381	9	—	1,916	24	1,778	93	138	7	—	6,284	79	5,724	91	560	9	—	3,617	45	3,280	91	337	9	—
AKI, stage 1	2,216	28	1,978	89	238	11	<0.001	2,816	35	2,572	91	244	9	0.07	1,153	14	1,000	87	153	13	<0.001	2,902	36	2,622	90	280	10	0.65
AKI, stage 2	596	7	506	85	90	15	<0.001	2,116	26	1,887	89	229	11	<0.001	177	2	157	88	20	11	0.27	369	5	341	92	28	8	0.27
AKI, stage 3	482	6	366	76	116	23	<0.001	1,130	14	916	81	214	19	<0.001	364	5	272	75	92	25	<0.001	1,090	14	910	83	180	16	<0.001

p Values reported for comparison patients with denoted stage with those without AKI.
AKI, acute kidney injury; MDRD, Modified Diet of Renal Diseases.