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Estimating baseline kidney function in hospitalized adults with acute kidney injury

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Abstract

Aim: Baseline serum creatinine values are required to diagnose acute kidney injury but are often unavailable. We evaluated four conventional equations to estimate creatinine. We then developed and validated a new equation corrected by age and gender.

Methods: We retrospectively examined adults who, at first hospital admission, had available baseline creatinine data and developed acute kidney injury ≥24 h after admission. We split the study population: 50% (derivation) to develop a new linear equation and 50% (validation) to compare against conventional equations for bias, precision, and accuracy. We stratified analyses by age and gender.

Results: We studied 3139 hospitalized adults (58% male, median age 71). Conventional equations performed poorly in bias and accuracy in patients aged <60 or ≥75 (68% of the study population). The new linear equation had less bias and more accuracy. There were no clinically significant differences in precision. The median (95% confidence interval) difference in creatinine values estimated via the new equation minus measured baselines was 0.9 (−3.0, 5.9) and −0.5 (−7.0, 3.7) μmol/L in female patients 18–60 and 75–100, and −1.5 (−4.2, 2.2) and −7.8 (−12.7, −3.6) μmol/L in male patients 18–60 and 75–100, respectively. The new equation improved reclassification of KDIGO AKI stages compared to the MDRD II equation by 5.0%.

Conclusion: Equations adjusted for age and gender are less biased and more accurate than unadjusted equations. Our new equation performed well in terms of bias, precision, accuracy, and reclassification.

KEYWORDS
acute kidney injury/diagnosis, acute kidney injury/epidemiology, age distribution, humans, linear models, sex distribution

Summary at a Glance

There are several ways to estimate baseline creatinine values for hospitalized patients at risk of acute kidney injury (AKI). Conventional approaches use rearranged versions of the MDRD II or CKD-EPI equations, substituting a fixed glomerular

filtration rate of 75 ml/min/1.73 m^2 to back-estimate creatinine. We found these approaches produced biased estimates in patients <60 or ≥75 years old. Because of this, we developed and validated new age- and gender-adjusted equations to estimate creatinine baseline values. These new equations performed better in bias, precision, and accuracy and improved reclassification of KDIGO AKI stages.

1 | INTRODUCTION

Acute kidney injury (AKI) is a complex syndrome characterized by an abrupt reduction in glomerular filtration rate (GFR). It occurs in up to 15% of hospital inpatients and is the source of considerable morbidity and mortality.[1,2] Patients who develop AKI have an increased risk of prolonged hospitalization, intensive care unit (ICU) admission, requirement for post-acute care, early readmission, chronic kidney disease (CKD), and death, both during and after the acute event.[2–6]

Identifying AKI using the current consensus criteria requires an estimation of baseline serum creatinine level as reference.[7–9] Regrettably, many patients have no serum creatinine level recorded in the 6–12 months prior to hospital admission. Moreover, where available, pre-admission measurements may be biased if performed during an intercurrent illness. This presents the problem of ascertaining AKI rate in patients without a baseline serum creatinine value.[10]

Previous studies have tried to resolve this issue by assuming a baseline eGFR of 75 ml/min/1.73 m^2 and rearranging the Modification of Diet in Renal Disease (MDRD II) study[9,11–14] or the CKD Epidemiology Collaboration (CKD-EPI) study equations to estimate baseline serum creatinine value.[15] This approach has been recommended by the both the Kidney Disease Improving Global Outcomes (KDIGO) Guideline for AKI and the Acute Dialysis Quality Initiative (ADQI). However, the MDRD-II equation was created using data from patients with CKD, and the CKD-EPI equation was created using data from patients both with and without CKD. Thus, they have never been validated for the purpose of estimating baseline creatinine to diagnose AKI.[16] Furthermore, assuming the presence of such a fixed eGFR for all patients will likely lead to overestimation of serum creatinine in younger patients and underestimation of serum creatinine in older patients, because GFR decreases with age.[17]

Our study had three aims:

1. In hospitalized patients, to evaluate the performance of conventional equations to estimate baseline serum creatinine value based on rearranging MDRD-II and CKD-EPI equations and assuming a fixed GFR of 75 ml/min/1.73 m^2.
2. In hospitalized patients, to derive new equations to estimate baseline serum creatinine value adjusted for age and gender from data obtained from hospitalized adults without advanced CKD.
3. In hospitalized patients, to compare the performance of these equations to that of the conventional equations.

2 | METHODS

2.1 | Study design and data sources

This was a retrospective observational study at Austin Health, a teaching hospital in Melbourne, Australia. We extracted patient records from the Clinical Research Data Warehouse (CRDW), which stores laboratory results for all patients in the hospital. These data included patient demographics, hospital admission and discharge characteristics (treating team, admission type, length of stay, care type), laboratory results, medical diagnoses, procedures, medications, and initiation of renal replacement therapy.

Ethics approval was obtained prior to commencement (LNR/18/Austin/286) and the need for informed consent was waived. All reporting was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18]

2.2 | Study population

We included all hospitalized adults (aged 18–100 years) who developed AKI at least 24 h into their index admission and had two or more available serum creatinine measurements during the study period, from 28 April 2011 when the earliest serum creatinine results were stored in the clinical research data warehouse through 12 November 2019.[19]

We defined the "Index Admission" as the first recorded hospital stay ≥ 24 h in duration for each patient. AKI was diagnosed using the serum creatinine component of the KDIGO criteria; urine output criteria were not assessed.[16]

We excluded all patients with no available baseline serum creatinine value (using the approach outlined below), as well as patients who developed AKI within the first 24 h of their index admission, and those with a primary admission to a palliative care unit. We also excluded patients who had undergone a nephrectomy or kidney transplant because of the unique immunological factors in transplant patients and reduced renal functional reserve in both groups.[20,21]

We excluded patients with a history of chronic kidney disease, including chronic dialysis patients and those who had a baseline serum creatinine ≥ 400 μmol/L,[22] because of their high creatinine baseline values and significant heterogeneity in their disease state and progression. Additionally, we excluded patients with intrinsic kidney

disease (i.e., glomerulonephritis or lupus nephritis) because of the unique pathogenesis of these diseases compared to other causes of AKI,[23] including complex immunological conditions, frequent association with underlying chronic kidney disease, the requirement for a kidney biopsy, and frequently the requirement for aggressive treatment.

2.3 | Computation of actual baseline serum creatinine from available values

To compute a baseline serum creatinine value for each patient from available values, we adapted the "method A" approach used in the Sapphire study,[19] referred to hereafter as the hybrid approach (Sapphire-adapted). The process was as follows.

All available serum creatinine values were extracted for each patient from the 6 months before the start of their index admission through to their discharge from hospital. These values were separated into three periods:

- *Period A*: The time period ≤6 months through >5 days before the index admission.
- *Period B*: The time period ≤5 days before the index admission through to the start of the index admission.
- *Period C*: The time period from the start of the index admission through to discharge.

A baseline serum creatinine value was calculated for each patient as follows:

- *median* of the values in Period A, if A had at least 5 values *or* more values than B; otherwise,
- *nadir* of the values in Period B, if B had at least one value; otherwise,
- *earliest* of the values in Period C.

2.4 | Conventional equations to estimate baseline serum creatinine

We examined four conventional equations to estimate baseline serum creatinine level. First, we rearranged the MDRD-II and CKD-EPI equations to back-estimate serum creatinine using estimated glomerular filtration rate 75 ml/min/1.73 m². Second, because glomerular filtration rate changes with age, we also included versions of the age- and gender-modified MDRD II and CKD-EPI equations. Recently, Fenton et al.[17] studied glomerular filtration rates measured before kidney donation in 2974 prospective living kidney donors across 18 centres in the United Kingdom. We used this data to estimate GFR based on age and gender, and then substituted the estimated GFR values into the rearranged MDRD-II and CKD-EPI equations. These equations (MDRD-75, CKD-EPI-75, MDRD-Fenton, and CKD-EPI-Fenton, respectively), and the method to estimate GFR based on Fenton et al., are shown in Table 1.

We used the CKD-EPI equation from 2009 in this study.[15] Another CKD-EPI equation was published in November 2021 to estimate GFR without incorporating race or ethnicity,[24] and we evaluated this new equation using the same approach (see Section 3 and Supporting information S1 for details).

2.5 | Derivation and validation datasets

We randomly assigned patients to either the derivation or validation datasets (50%–50%). We used a derivation dataset to generate new equations to estimate baseline serum creatinine values for patients (see Supporting information for details). We evaluated the performance of these equations using a validation dataset, comparing the accuracy, bias, and precision of our new equations against existing equations (MDRD-75, CKD-EPI-75, MDRD-Fenton, CKD-EPI-Fenton).

2.6 | Statistical analysis

We described the demographic and clinical characteristics of patients in both datasets using frequencies and percentages for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Missing data were not imputed. We developed our linear equation by fitting a linear model with serum creatinine as the response variable and age and gender as the input variables, exclusively from the derivation dataset.

We calculated the bias, precision, and accuracy of each equation for the estimation of baseline kidney function. We used the median of the differences between computed "actual" and estimated values to calculate bias, the interquartile range of the differences to calculate precision, and the percentage of estimates falling within 30% under/ above the actual baseline to calculate accuracy. We reported each metric by age and gender groups and the 95% confidence intervals for each metric using bootstrapping with 10 000 repetitions.

We examined the implications of each equation on the accuracy of KDIGO AKI stage classification, comparing the actual KDIGO AKI stage according to the actual baseline value compared to the KDIGO AKI stage resulting from the estimates generated by each equation.

We considered the robustness of results via subgroup analyses to determine how varying different conditions could affect results. We looked at four subgroups: (1) patients whose baseline serum creatinine was computed as the median of serum creatinine measurements in the time period ≤6 months through >5 days before the index admission; (2) patients whose baseline serum creatinine was computed as the nadir of serum creatinine measurements in the time period ≤5 days through the time of the index admission; (3) patients whose baseline serum creatinine was computed as the earliest of serum creatinine measurements in the time period from the index admission (≥0 h) through the time of discharge; and (4) patients whose baseline serum creatinine values fell into the gender specific

TABLE 1 Equations to estimate serum creatinine

Reference	Explanation	Equation to estimate serum creatinine (μmol/L)
New-LE	New linear equation to estimate baseline serum creatinine.	$55.2 + 0.525 \times \text{age} - (15.0 \text{ if female})$
CKD-EPI-75 and CKD-EPI-Fenton	Rearranged Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate serum creatinine. For CKD-EPI-75, substitute eGFR = 75 ml/min/1.73 m². For CKD-EPI-Fenton, substitute eGFR = estimated GFR mL/min/1.73 m² based on age and gender using values derived from Fenton et al.[a]	Female patients: • When result is <61.88, $88.4 \times \dfrac{2.519 \times 10^6 \times 1.00705^{-3 \times \text{age}}}{\text{eGFR}^3 \times (1.00705^{\text{age}} \times \text{eGFR})^{13/329}}$ • When result is ≥61.88, $88.4 \times \dfrac{42.5784}{(1.00705^{\text{age}} \times \text{eGFR})^{\frac{1000}{1209}}}$ Male patients: • When result is <79.56, $88.4 \times \dfrac{152576 \times 1.00705^{-2 \times \text{age}}}{\text{eGFR}^2 \times (1.00705^{\text{age}} \times \text{eGFR})^{178/411}}$ • When result is ≥79.56, $88.4 \times \dfrac{53.9418}{(1.00705^{\text{age}} \times \text{eGFR})^{1000/1209}}$
MDRD-75 and MDRD-Fenton	Rearranged Modification of Diet in Renal Disease (MDRD) II equation to estimate serum creatinine. For MDRD-75, substitute eGFR = 75 ml/min/1.73 m². For MDRD-Fenton, substitute eGFR = estimated GFR mL/min/1.73 m² based on age and gender using values derived from Fenton et al.[a]	Female patients: • $88.4 \times \dfrac{(175^{0.867}) \times 0.772}{(\text{age}^{0.203} \times \text{eGFR})^{0.867}}$ Male patients: • $88.4 \times \dfrac{175^{0.867}}{(\text{age}^{0.203} \times \text{eGFR})^{0.867}}$
Gender-fixed	Mean value in reference range[b] for female and male patients with no age component.	Female patients: 70.0 Male patients: 85.0

Abbreviations: eGFR, estimated glomerular filtration rate.

[a]Using the study data from Fenton et al., we estimated GFR as follows: when age <35 years, female eGFR = 99 and male eGFR = 100; when age ≥ 35 years, female eGFR = 127.0–0.8 × age and male eGFR = 122.7152–0.6594 × age.[17]

[b]Serum creatinine reference range according to British Medical Journal (BMJ) Best Practice.[25]

reference ranges for creatinine of 45–90 μmol/L for female patients and 60–110 μmol/L for male patients.[25]

3 | RESULTS

3.1 | Patient demographics and clinical characteristics

We included 3139 patients (out of 226 433 patients with a serum creatinine measurement). Of these, we randomly selected 1569 for the derivation dataset and 1570 for the validation dataset. We show the study flow diagram in Figure 1 and equations to estimate baseline serum creatinine in Table 1.

Table 2 summarizes the baseline characteristics of the study population. Forty-two percent of patients were female. Their median age was 71 years (interquartile range [IQR] 58, 80). Most patients (81%) had stage 1 AKI, while 10% of patients had stage 2 AKI and 9% had stage 3 AKI. Patients spent a median of 11 days (IQR 6, 21) in hospital. About 45% of patients were admitted to the ICU, and these patients had a median length of ICU stay for 3 days (IQR 1, 8).

3.2 | Computation of actual baseline serum creatinine values and glomerular filtration rates according to different selection choices

We used the hybrid approach (see above) to compute a single "actual" baseline value from multiple measured creatinine values for each patient. Table 3 compares three approaches for computing baselines from measured values: (1) the hybrid method used in this study (which uses pre-admission data where possible, and the median, minimum, or earliest of values depending on available data); (2) the minimum post-admission serum creatinine measurement in the hospital; (3) and the median post-admission serum creatinine measurement in the hospital. For methods 1–3, we estimated GFR using the MDRD II equation with the computed "actual" creatinine baselines from each method. For comparison, we included (4) the back-estimated creatinine from the rearranged MDRD II equation with a fixed value of eGFR = 75 ml/min/1.73 m² (MDRD-75). Methods 1–3 computed creatinine baselines from measured values and used them to estimate GFR, while method 4 instead assumed a fixed GFR and used it to back-estimate creatinine.

We found that MDRD-75 (method 4) produced biased estimates which differed substantially from baselines obtained using measured
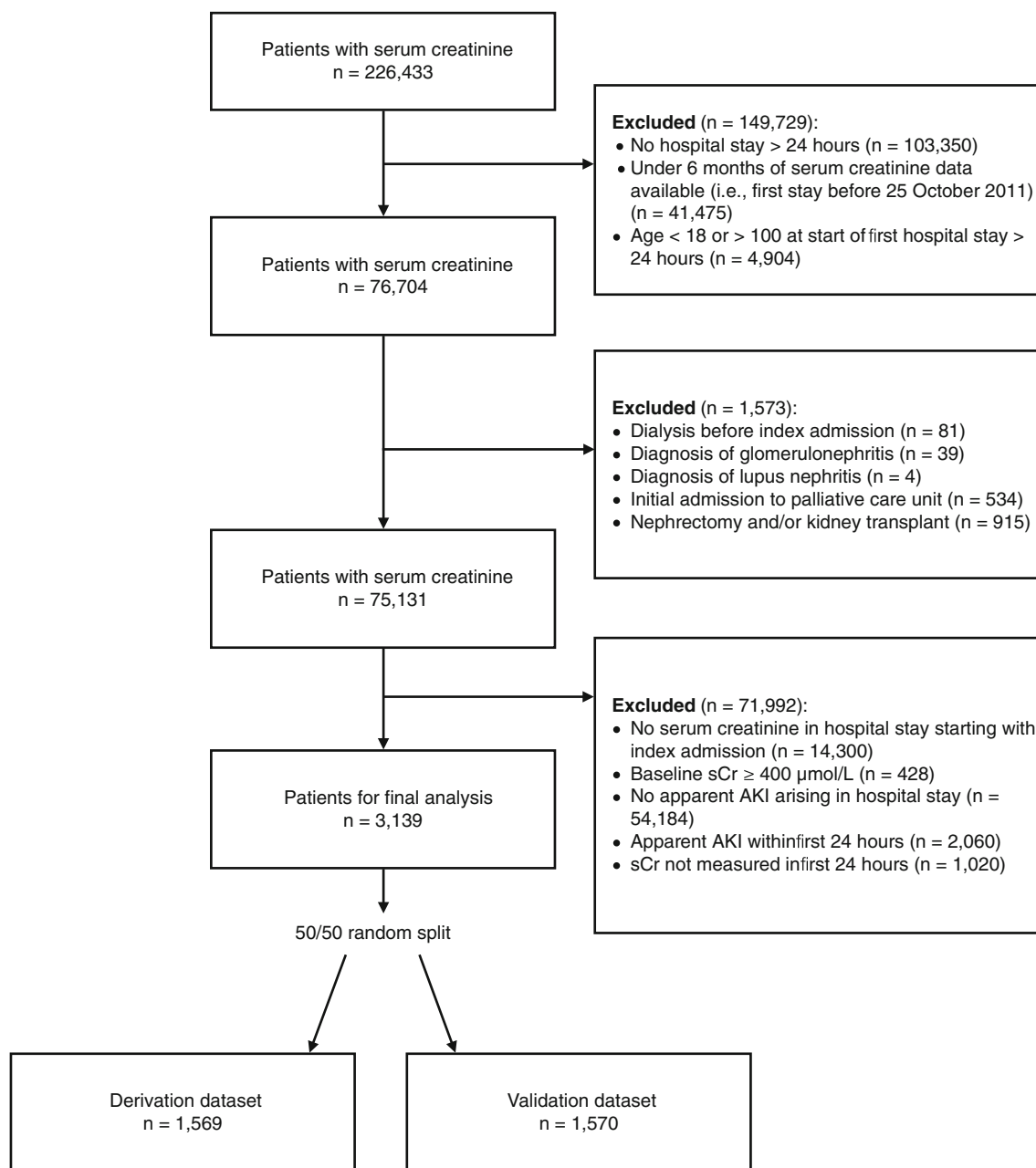
FIGURE 1 Study flow diagram. Patients' index admission was defined as their first admission to hospital with a stay over 24 h. Beginning with 226 433 patients with at least one serum creatinine value in the clinical research data warehouse, we excluded in this order: 103350 with no hospital stay over 24 h; 41 475 with a first stay before 25 October 2011 (i.e., within 6 months after creatinine results first began to flow into the data warehouse); 4904 aged <18 or >100 at their index admission; 81 with dialysis at any time before index admission; 39 with diagnosis of glomerulonephritis; 4 with diagnosis of lupus nephritis; 534 with initial admission to the palliative care unit; 915 with record of nephrectomy and/or kidney transplant; 14 300 with no serum creatinine in the hospital stay beginning with first index hospital admission; 428 with a baseline serum creatinine value over 400 μmol/L; 54 184 with no apparent acute kidney injury during the hospital stay; 2060 with apparent acute kidney injury within 24 h from admission; and 1020 with no serum creatinine measurement in the first 24 h from admission. This left 3139 patients in the study cohort. We then randomly split these patients 50%/50% into derivation/validation cohorts with 1569/1570 patients respectively

values (according to methods 1–3). For patients aged 18 to <60, estimates from MDRD-75 were on average ~10 μmol/L *higher* than determined from measured values using the hybrid method, whereas for patients aged 75–100, the estimates were ~20 μmol/L *lower*. Only in patients aged 60 to <75 were the MDRD-75 estimates and baselines from measured values using the hybrid method approximately the same.

These differences affect classification of KDIGO AKI stages. For example, a patient with a known baseline of 87 μmol/L according to the hybrid approach would meet the KDIGO criteria for AKI once their creatinine levels reached ≥113.5 or 130.5 μmol/L (within 48 h or 7 days, respectively). However, this patient could be assigned a low baseline of 65 μmol/L by MDRD-75, and thus meet the KDIGO criteria for AKI

TABLE 2 Baseline characteristics of the study population

Characteristic	Overall (100%)	Derivation (50%)	Validation (50%)
Patients, no.	3139	1569	1570
Female, no. (%)	1316 (42)	670 (43)	646 (41)
Age, median (IQR), years	71 (58, 80)	71 (59, 80)	71 (58, 80)
Age range, no. (%), years			
18 to <60	855 (27)	424 (27)	431 (27)
60 to <75	996 (32)	496 (32)	500 (32)
75 to 100	1288 (41)	649 (41)	639 (41)
Serum creatinine, median (IQR) (μmol/L)			
Baseline	85.0 (67.0, 113.0)	86.0 (67.0, 115.0)	85.0 (67.0, 112.0)
Peak in stay	137.0 (109.0, 189.0)	139.0 (109.0, 187.0)	136.0 (110.0, 191.0)
Nadir in stay	74.0 (56.0, 99.0)	74.0 (55.0, 99.0)	74.0 (57.0, 98.0)
Median in stay	99.0 (76.0, 131.2)	99.0 (75.0, 132.0)	99.0 (76.0, 130.4)
Peak minus baseline absolute increase	42.0 (31.0, 69.0)	41.0 (31.0, 67.0)	42.0 (31.0, 73.0)
Peak minus baseline relative % increase	51.9 (37.0, 79.2)	51.4 (36.5, 78.5)	52.2 (37.7, 80.4)
KDIGO AKI stage, no. (%)			
Stage 1 AKI	2533 (81)	1279 (82)	1254 (80)
Stage 2 AKI	321 (10)	149 (9)	172 (11)
Stage 3 AKI	285 (9)	141 (9)	144 (9)
Time from admission to events, median (IQR) (h)			
First serum creatinine in stay	6.3 (1.7, 12.5)	6.0 (1.6, 12.8)	6.6 (1.7, 12.3)
First apparent AKI detection	80.9 (44.2, 163.9)	81.2 (45.6, 165.5)	80.2 (43.0, 163.2)
Discharge from hospital (length of stay)	269.0 (151.0, 505.0)	281.0 (156.0, 509.0)	261.0 (148.0, 499.0)
Intensive care unit (ICU) admission			
Admitted to ICU, no. (%)	1376 (44)	701 (45)	675 (43)
Time in ICU, median (IQR) (h)	0.0 (0.0, 63.5)	0.0 (0.0, 68.0)	0.0 (0.0, 55.8)

Abbreviation: IQR, interquartile range. Units: Serum creatinine in μmol/L; to convert to mg/dl, divide by 88.4.

once their creatinine levels reached ≥91.5 or 97.5 μmol/L (within 48 h or 7 days, respectively), a rise of only 4.5 to 10.5 μmol/L above their actual baseline. In reclassification analyses (see below), we found that addressing the bias in creatinine estimates using a new equation improved reclassification of KDIGO AKI stages compared to the MDRD II equation by 5.0% overall.

3.3 | Performance of equations to estimate serum creatinine

We compared the performance of different equations to estimate serum creatinine in the validation dataset. To do this, we estimated baseline creatinine values for each patient using the equations defined in Table 1 and computed actual baseline creatinine values from measurements for each patient using the hybrid approach defined above. We assessed bias as the median difference between the actual values for baseline serum creatinine and the estimated values, precision as the interquartile range (IQR) of the difference between the actual and estimated baseline serum creatinine values, and accuracy as the percentage of estimates within 30% of the actual baseline serum creatinine value.

Table 4 and Figure 2 show the bias, precision, and accuracy of the equations in the validation dataset.

3.4 | Bias

The CKD-EPI-75 and MDRD-75 equations were strongly biased for both female and male patients. Both equations tended to overestimate serum creatinine in patients aged 18–60 years and underestimate serum creatinine in patients aged 75–100 years.

By contrast, the age- and gender-adjusted CKD-EPI-Fenton and MDRD-Fenton equations had less bias, although they still overestimated serum creatinine in patients aged 18–60 years and underestimated serum creatinine in patients aged 75–100 years. The gender-fixed serum creatinine estimates had similar bias to the CKD-EPI-Fenton equation.

Our novel linear equation (New-LE), developed on the derivation dataset, had the least bias of all the equations. The New-LE equation had a median error of 0.9 (95% confidence interval −3.0, 5.9) μmol/L in female patients aged 18–60 years, and a median error of −0.5 (−7.0, 3.7) μmol/L in female patients aged 75–100 years. In males, the

TABLE 3 Comparison of methods to compute baseline serum creatinine when serum creatinine measurements are available

Method used to obtain baseline	Baseline serum creatinine, median (IQR), μmol/L		Baseline estimated GFR,[a] median (IQR), ml/min/1.73 m²
Female patients (n = 1316)			
1: Hybrid (Sapphire-adapted) approach[b]	76.0 (57.0, 104.0)	→	64.7 (45.2, 94.3)
2: Minimum in-hospital value since admission	64.0 (47.8, 91.0)	→	79.6 (52.0, 117.5)
3: Median in-hospital value since admission	89.8 (67.0, 123.0)	→	53.7 (37.4, 77.7)
4[c]: Unchanging eGFR = 75 ml/min/1.73 m²	66.9 (65.5, 69.6)	←	75.0 (75.0, 75.0)
Male patients (n = 1823)			
1: Hybrid (Sapphire-adapted) approach[b]	91.0 (75.0, 119.0)	→	72.3 (52.8, 91.8)
2: Minimum in-hospital value since admission	80.0 (63.0, 104.0)	→	84.1 (61.6, 112.0)
3: Median in-hospital value since admission	104.5 (84.0, 136.0)	→	61.7 (44.7, 81.2)
4[c]: Unchanging eGFR = 75 ml/min/1.73 m²	87.5 (85.4, 90.2)	←	75.0 (75.0, 75.0)

Note: Arrows: For methods 1–3, the → right-arrow indicates creatinine baselines were first calculated from measured values and then used in the MDRD II equation to estimate GFR. For method 4, the ← left-arrow indicates estimated GFR was held at a fixed value of 75 ml/min/1.73 m² and then used to estimate creatinine baseline without using any measured values.

Abbreviations: IQR, interquartile range; GFR, glomerular filtration rate.

[a]Estimated glomerular filtration rate (GFR) from serum creatinine values using the MDRD II equation eGFR ml/min/1.73 m² = $175 \times$ (serum creatinine mg/dl)$^{-1.154} \times$ (age)$^{-0.203} \times$ (0.742 if female) $\times$ (1.212 if African-American). Divide serum creatinine in μmol/L by 88.4 to obtain serum creatinine in mg/dl.

[b]Hybrid (Sapphire-adapted) approach: Baseline serum creatinine values obtained using the approach described in the Methods section of this article, which was adapted from the Sapphire study.[19] This is the technique we use in this study.

[c]For method 4, we assumed baseline eGFR was 75 ml/min/1.73 m² and then back-estimated serum creatinine using the MDRD-75 equation (see Table 1). This differed from methods 1–3, where we first calculated baseline serum creatinine and then used it to obtain eGFR in the MDRD II equation.

median error was −1.5 (−4.2, 2.2) μmol/L in patients aged 18–60 years, and −7.8 (−12.7, −3.6) in patients aged 75–100 years.

New-LE performed better than other equations in terms of bias in most age groups for both female and male patients. There was, however, one exception: for female patients aged 60 to <75 (27.1% of female patients and 11.1% of all patients in the validation dataset). In these patients, the New-LE equation produced higher creatinine estimates than baseline values (median error 8.5 [95% confidence interval 2.0, 12.4] μmol/L and other equations. Further research is needed to enhance the performance of the model in female patients aged 60 to <75, accounting for sources of difference including timing of onset and progression of comorbidities (e.g., diabetes and hypertension) and cardiac surgery (a known risk factor for AKI). This is because female patients were less likely than male patients to undergo cardiac surgery in this age group (38 [19.5%] vs. 84 [27.9%], respectively). Other factors may have affected these findings, such as reduction in muscle mass after menopause; use of medications at home; and survivorship bias introduced by the inclusion of older male patients in the training dataset. Notably, the New-LE equation performed better than all other equations in terms of bias in all the other groups split by age group and gender (which comprised 88.9% of the validation dataset).

3.5 | Precision

There were no clinically significant differences in precision between equations. Precision was best in patients aged 60–75 years, with an interquartile range (IQR) of differences of 36.0 (95% confidence interval 28.0, 46.5) μmol/L in female patients and 34.8 (30.3, 40.8) μmol/L in male patients using the New-LE equation.

3.6 | Accuracy

As with bias, the accuracy of equations differed depending on the age group for both female and male patients. In patients aged 18–60 who made up 27% of the validation dataset, the MDRD-Fenton and New-LE equations were the most accurate. In patients aged 60–75 who made up 32% of the validation dataset, there was no clinically significant difference in accuracy between equations. In patients aged 75–100 who made up 41% of the validation dataset, the New-LE, MDRD-Fenton, and CKD-EPI-Fenton equations were the most accurate.

3.7 | Performance with CKD-EPI (2009) compared with CKD-EPI (2021)

The CKD-EPI equation used in this study was published in 2009.[15] Another version of the equation to estimate GFR without incorporating race or ethnicity was published in November 2021.[24] Bias, precision, and accuracy of creatinine estimates were similar for both the 2009 and 2021 versions of the CKD-EPI equation (see Table S7 and Figure S5).

TABLE 4 Bias, precision, and accuracy of equations to estimate baseline serum creatinine in the validation dataset

Group and equation[a]	Bias[b] (95% CI) (μmol/L)	Precision[c] (95% CI) (μmol/L)	Accuracy[d] (95% CI) (%)
Female patients aged 18 to <60			
CKD-EPI-75	17.6 (10.8, 23.0)	47.1 (35.7, 61.3)	35.0 (27.7, 41.8)
CKD-EPI-Fenton	6.0 (1.4, 13.2)	47.0 (32.0, 61.5)	37.3 (29.9, 44.6)
MDRD-75	8.4 (3.5, 15.7)	47.1 (34.5, 61.4)	36.7 (29.9, 44.1)
MDRD-Fenton	0.0 (−5.3, 6.6)	47.2 (31.8, 61.9)	46.3 (39.0, 53.7)
New-LE	0.9 (−3.0, 5.9)	44.5 (31.3, 59.8)	46.3 (39.0, 53.7)
Gender-fixed	5.0 (1.0, 13.0)	45.0 (31.0, 61.0)	38.4 (31.1, 45.8)
Female patients aged 60 to <75			
CKD-EPI-75	4.0 (−0.4, 8.1)	36.8 (30.2, 45.4)	56.6 (49.1, 64.0)
CKD-EPI-Fenton	5.7 (0.5, 10.6)	36.7 (28.4, 46.2)	54.9 (47.4, 62.3)
MDRD-75	0.5 (−4.1, 3.9)	36.4 (29.4, 45.6)	54.3 (46.9, 61.7)
MDRD-Fenton	2.2 (−4.3, 6.4)	36.1 (28.0, 46.4)	54.9 (47.4, 62.3)
New-LE	8.5 (2.0, 12.4)	36.0 (28.0, 46.5)	53.7 (46.3, 61.1)
Gender-fixed	3.0 (−2.5, 7.0)	37.0 (29.0, 46.0)	56.0 (48.6, 62.9)
Female patients aged 75 to 100			
CKD-EPI-75	−21.1 (−27.1, −16.5)	46.9 (38.4, 55.8)	48.6 (42.9, 54.4)
CKD-EPI-Fenton	−6.3 (−12.5, −1.8)	43.8 (37.3, 52.6)	59.9 (54.1, 65.3)
MDRD-75	−20.5 (−26.9, −15.8)	45.8 (37.8, 54.1)	50.7 (44.9, 56.5)
MDRD-Fenton	−4.9 (−10.2, −1.5)	43.2 (37.0, 51.9)	58.5 (52.7, 64.3)
New-LE	−0.5 (−7.0, 3.7)	43.7 (37.0, 52.4)	57.1 (51.4, 62.9)
Gender-fixed	−15.0 (−22.0, −11.0)	45.5 (37.8, 53.5)	55.4 (49.7, 61.2)
Male patients aged 18 to <60			
CKD-EPI-75	21.2 (18.0, 24.7)	32.1 (26.1, 38.3)	46.9 (40.9, 52.8)
CKD-EPI-Fenton	6.4 (3.6, 9.4)	30.9 (26.5, 39.0)	61.0 (55.1, 66.9)
MDRD-75	12.7 (10.9, 16.9)	31.3 (25.9, 38.3)	56.7 (50.8, 62.6)
MDRD-Fenton	−1.4 (−3.7, 1.8)	31.5 (26.6, 38.5)	68.5 (62.6, 74.4)
New-LE	−1.5 (−4.2, 2.2)	33.3 (27.3, 38.4)	64.6 (58.3, 70.5)
Gender-fixed	5.0 (2.0, 7.0)	31.0 (25.8, 38.0)	63.0 (57.1, 68.9)
Male patients aged 60 to <75			
CKD-EPI-75	0.5 (−2.0, 5.0)	37.6 (30.5, 42.2)	68.9 (64.0, 73.8)
CKD-EPI-Fenton	−2.3 (−5.7, −0.3)	35.8 (30.5, 41.9)	70.5 (65.5, 75.4)
MDRD-75	−2.5 (−4.6, 0.9)	36.4 (30.6, 41.9)	71.7 (66.8, 76.6)
MDRD-Fenton	−5.0 (−9.0, −2.3)	35.0 (30.6, 41.4)	72.0 (67.1, 76.9)
New-LE	0.9 (−3.6, 3.8)	34.8 (30.3, 40.8)	68.0 (62.8, 73.2)
Gender-fixed	−5.0 (−8.0, −2.5)	36.0 (30.0, 42.0)	72.0 (67.1, 76.9)
Male patients aged 75 to 100			
CKD-EPI-75	−23.7 (−26.8, −17.3)	51.0 (44.0, 61.0)	59.1 (53.9, 64.3)
CKD-EPI-Fenton	−15.8 (−21.1, −12.1)	51.2 (42.6, 59.8)	64.1 (58.8, 69.0)
MDRD-75	−21.2 (−26.4, −16.3)	50.8 (43.6, 61.0)	60.0 (54.5, 65.2)
MDRD-Fenton	−14.1 (−19.1, −9.7)	50.4 (41.7, 57.2)	64.1 (59.1, 69.3)
New-LE	−7.8 (−12.7, −3.6)	50.6 (41.8, 57.4)	64.9 (60.0, 69.9)
Gender-fixed	−20.0 (−26.0, −16.0)	51.0 (43.0, 61.0)	61.4 (56.2, 66.7)

Abbreviations: sCr, serum creatinine; CI, confidence interval. Units: Serum creatinine in μmol/L; to convert to mg/dl, divide by 88.4.
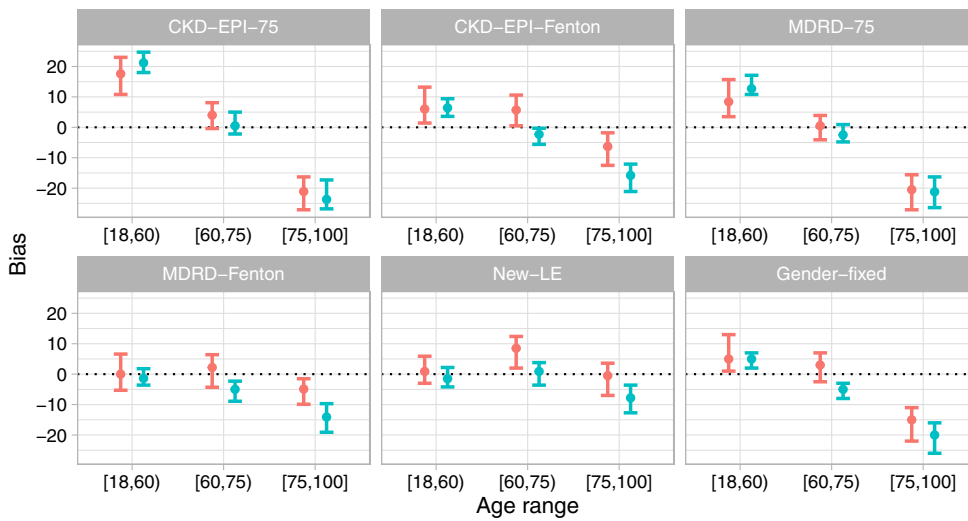
[a]Estimation equation: Table 1 shows the different equations used to estimate baseline serum creatinine.

[b]Bias: Median difference between estimated serum creatinine values for patients obtained using an equation minus known baseline values for the patient (both in μmol/L).
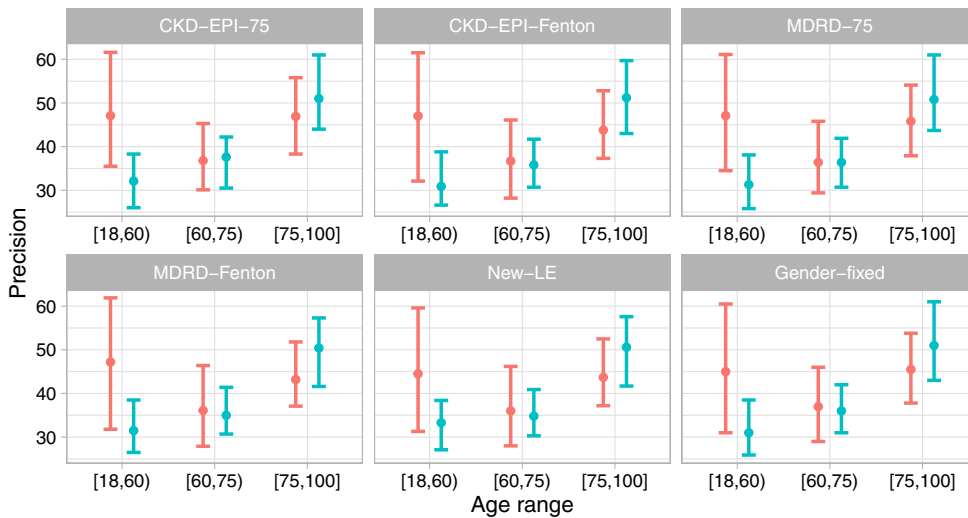
[c]Precision: Interquartile range (distance between 25th–75th percentiles) of differences obtained as described for "Bias."

[d]Accuracy: Percentage of estimated serum creatinine values within 30% of known baseline values as described for "Bias."

(A) Bias

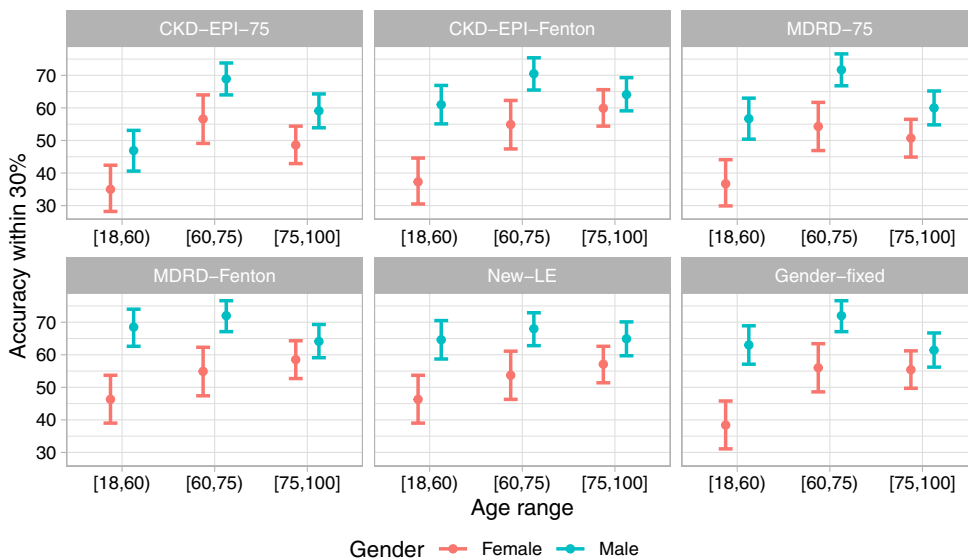## (B) Precision

(C) Accuracy within 30%

FIGURE 2 Bias, precision, and accuracy of equations to estimate baseline serum creatinine in the validation dataset. Performance metrics on the validation dataset for each serum creatinine estimation equation, by age group and gender. For the equation definitions, see Table 1. Panel A: Bias (95% confidence interval), μmol/L. Median difference between estimated serum creatinine values for patients obtained using an equation minus known baseline values for the patient (both in μmol/L). Panel B: Precision (95% confidence interval), μmol/L. Interquartile range (distance between 25th and 75th percentiles) of differences obtained as described for "Bias." Panel C: Accuracy (95% confidence interval), %. Accuracy defined as the percentage of estimated serum creatinine values within 30% of known baseline values as described for "Bias." Serum creatinine in μmol/L; to convert to mg/dl, divide by 88.4

TABLE 5 Reclassification of KDIGO AKI stage using back-estimated serum creatinine from the MDRD II equation with eGFR = 75 ml/min/1.73 m² (MDRD-75) to estimated serum creatinine from the new linear equation (New-LE) in the validation dataset, by actual AKI stage

Characteristic	Overall	Stage 1 AKI	Stage 2 AKI	Stage 3 AKI
Patients, no.	1570	1254	172	144
Reclassified[a], no. (%)	419 (26.7)	346 (27.6)	52 (30.2)	21 (14.6)
Better classification[b], no. (%)	249 (15.9)	208 (16.6)	31 (18.0)	10 (6.9)
Worse classification[c], no. (%)	170 (10.8)	138 (11.0)	21 (12.2)	11 (7.6)
Net difference, no. (%), p value	79 (5.0), $p < 0.001$	70 (5.6), $p < 0.001$	10 (5.8), $p = 0.189$	−1 (−0.7), $p = 0.923$

[a]Reclassification: New-LE equation led to a different AKI classification than the MDRD-75 equation. We obtained serum creatinine estimates for patients in the validation dataset using the MDRD-75 and New-LE equations, which are listed in Table 1. We used these estimates along with patients' known baseline creatinine values to classify acute kidney injury stage in these patients according to the KDIGO guidelines (no apparent AKI or stage 1, 2, or 3 AKI).
[b]Better classification: New-LE equation led to an estimated AKI stage closer to the actual AKI stage than the MDRD-75 equation.
[c]Worse classification: New-LE equation led to an estimated AKI stage further from the actual AKI stage than the MDRD-75 equation.

3.8 | Reclassification of KDIGO AKI stages using estimates derived from equations

Table 5 compares the reclassification accuracy of the New-LE equation against the MDRD-75 equation using estimated serum creatinine values from the New-LE and MDRD-75 equations and patients' measured serum creatinine. We classified patients according to the KDIGO AKI criteria using both equations (estimated classifications) and measured creatinine (known classification).

In the validation dataset, 419 patients (26.7%) were reclassified by the New-LE equation to a different AKI stage than obtained using the MDRD-75 equation. Of these, 249 patients (15.9%) had a better classification (nearer or equal to the patient's known AKI stage), and 170 (10.8%) had a worse classification. Overall, the net improvement in reclassification of KDIGO AKI stages by the New-LE equation compared to the MDRD-75 equation was 5.0% ($p < 0.001$).

We also compared the reclassification accuracy of the MDRD-Fenton equation against the MDRD-75 equation using the same process (see Table S5). The net improvement in reclassification of KDIGO AKI stages by the MDRD-Fenton equation compared to the MDRD-75 equation was 4.5% ($p < 0.001$). Finally, we compared the reclassification accuracy of the New-LE equation against the MDRD-Fenton equation (Table S6) and found no statistically significant difference between reclassification of AKI stages, suggesting both equations have similar reclassification performance.

3.9 | Subgroup analyses

Table 6 summarizes the characteristics of patients in subgroups 1–4 in the validation dataset.

Bias, precision, and accuracy of the equations across subgroups 1, 2, 3, and 4 are presented in Tables S1a, S2a, S3a, and S4a, as well as Figures S1, S2, S3, and S4, respectively. Our findings were largely consistent across all subgroups tested with no clinically significant differences in bias, precision, or accuracy of equations in analyses of subgroups 1 to 3 compared to the primary analysis. In patients whose baseline creatinine value was within the reference ranges (subgroup

4), the New-LE was slightly more precise across all age groups than in the primary analysis, but also more biased for patients aged 75–100 years, tending to overestimate rather than underestimate values.

KDIGO AKI stage reclassification by the New-LE equation compared to the MDRD-75 equation for subgroups 1, 2, 3, and 4 are shown in Tables S1b, S2b, S3b, and S4b, respectively. In subgroup 1, the New-LE equation was slightly worse (−2.5% net improvement) but there were few reclassified patients, and in subgroup 4 the New-LE equation was worse than the MDRD-75 equation (−6.4% net improvement). The New-LE equation outperformed the MDRD-75 equation as in the primary analysis for subgroup 2 (8.0% net improvement) and subgroup 3 (5.5% net improvement).

4 | DISCUSSION

4.1 | Key findings

We derived and validated a novel linear equation to estimate baseline serum creatinine value in hospitalized patients at risk of AKI. This equation performed well against conventional approaches using MDRD and CKD-EPI equations (assuming a fixed eGFR of 75 ml/min/1.73 m²) as well as age- and gender-adjusted GFR values adapted from Fenton et al. Compared to these existing equations, our novel equation had the lowest bias, the highest precision, and the highest accuracy.

Our new equation improved reclassification of KDIGO AKI stages compared to the MDRD equation when using a fixed eGFR of 75 ml/min/1.73 m² for MDRD. By substituting age- and gender-adjusted GFR values in the MDRD equation, we improved the creatinine estimates so that both the adjusted MDRD and our novel equation had similar performance for reclassification of KDIGO AKI stages.

4.2 | Relationship to other studies

In the absence of a standard method to accommodate missing values, existing studies have used different approaches to substitute or

TABLE 6 Characteristics of patients in subgroups 1–4 in the validation dataset

Characteristic	Validation (overall)	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
Patients, no.	1570	275	589	706	942
Female, no. (%)	646 (41)	94 (34)	267 (45)	285 (40)	361 (38)
Age, median (IQR), years	71 (58, 80)	68 (58, 77)	74 (60, 83)	69 (57, 79)	69 (58, 78)
Age range, no. (%), years					
18 to <60	431 (27)	83 (30)	139 (24)	209 (30)	271 (29)
60 to <75	500 (32)	103 (37)	162 (28)	235 (33)	336 (36)
75 to 100	639 (41)	89 (32)	288 (49)	262 (37)	335 (36)
Serum creatinine, median (IQR), μmol/L					
Baseline	85.0 (67.0, 112.0)	86.0 (72.0, 102.5)	89.0 (67.0, 119.0)	83.0 (64.2, 108.8)	77.0 (65.6, 88.0)
Peak in stay	136.0 (110.0, 191.0)	135.0 (113.0, 179.0)	141.0 (109.0, 197.0)	134.0 (108.0, 189.5)	123.0 (106.0, 146.0)
Nadir in stay	74.0 (57.0, 98.0)	69.0 (58.0, 89.5)	80.0 (60.0, 110.0)	71.5 (52.0, 93.8)	67.0 (55.0, 80.0)
Median in stay	99.0 (76.0, 130.4)	93.0 (80.0, 119.5)	105.0 (79.0, 140.0)	95.2 (72.0, 126.0)	88.2 (73.5, 105.0)
Peak minus baseline absolute increase	42.0 (31.0, 73.0)	42.0 (32.0, 69.5)	41.0 (31.0, 73.0)	42.0 (31.0, 74.8)	40.0 (31.0, 64.0)
Peak minus baseline relative % increase	52.2 (37.7, 80.4)	50.0 (37.4, 85.2)	50.0 (36.5, 75.0)	55.0 (39.2, 84.1)	54.5 (41.5, 84.1)
KDIGO AKI stage, no. (%)					
Stage 1 AKI	1254 (80)	217 (79)	483 (82)	554 (78)	746 (79)
Stage 2 AKI	172 (11)	35 (13)	52 (9)	85 (12)	115 (12)
Stage 3 AKI	144 (9)	23 (8)	54 (9)	67 (9)	81 (9)
Time from admission to events, median (IQR) (h)					
First serum creatinine in stay	6.6 (1.7, 12.3)	8.6 (4.5, 12.4)	10.5 (4.8, 15.7)	2.5 (0.8, 7.9)	6.9 (1.7, 12.0)
First apparent AKI detection	80.2 (43.0, 163.2)	61.0 (39.7, 152.5)	69.7 (39.6, 136.8)	97.5 (49.3, 192.6)	82.2 (43.5, 168.9)
Discharge from hospital (length of stay)	261.0 (148.0, 499.0)	268.0 (158.0, 513.0)	214.0 (124.0, 424.0)	304.0 (173.0, 556.0)	264.5 (151.2, 525.8)
Intensive care unit (ICU) admission					
Admitted to ICU, no. (%)	675 (43)	168 (61)	179 (30)	328 (46)	462 (49)
Time in ICU, median (IQR), (h)	0.0 (0.0, 55.8)	23.0 (0.0, 79.0)	0.0 (0.0, 23.0)	0.0 (0.0, 65.8)	0.0 (0.0, 68.0)

Abbreviation: IQR, interquartile range. Units: Serum creatinine in μmol/L; to convert to mg/dl, divide by 88.4.

impute reference values. Until recently, the potential error introduced by use of these surrogates was unknown. Siew et al. found that the use of imputed (i.e., eGFR 75 ml/min/1.73 m^2) and minimum baseline serum creatinine values significantly inflated the likely incidence of AKI, producing low specificity, while the use of the admission creatinine value greatly underestimated its likely incidence, yielding a low sensitivity.[10] Our findings support the bi-directional misclassification of AKI using commonly used surrogates.

The previous KDIGO and ADQI recommendation that one should assume a fixed GFR value of 75 ml/min/1.73 m^2 tends to over-estimate baseline serum creatinine for younger patients (leading to potential under detection of AKI) and under-estimate baseline serum creatinine for older patients (leading to potential over detection of AKI).[16] Our findings reinforce the importance of using age- and gender-adjusted GFR values rather than a fixed GFR value (e.g., 75 ml/min/1.73 m^2) when estimating a reference value for serum creatinine.

The ability to accurately estimate a reference creatinine value is of clear importance in identifying patients who have developed AKI during an acute illness. Available methods to impute missing baseline creatinine values may be unreliable and inaccurate, while excluding patients who are missing a baseline creatinine value would introduce selection bias. Thus, there is a clear need for accurate, reliable, and generalisable methods to impute missing values so that clinicians can identify patients who have experienced AKI with both more accuracy and less bias.

4.3 | Implications of study findings

Our findings imply that a more accurate, less biased equation can be developed to estimate baseline creatinine values in hospitalized patients where such pre-admission information is not available (the

vast majority). Moreover, our findings suggest that estimates of baseline serum creatinine which do not consider age and gender are likely to be misleading, because assuming a fixed GFR value over-estimates baseline serum creatinine in younger patients and under-estimates baseline serum creatinine for older patients. Finally, they imply that, as demonstrated in this study, a methodology can be applied to develop such estimates that, at the very least, is more accurate and less biased in the population served by the study institution.

4.4 | Strengths and limitations

Our study draws on a large patient database and focuses on patients who went on to developed AKI rather than patients with normal kidney function or CKD or those being managed in outpatient clinics. Our findings are plausible and were robust across subgroup analyses. Furthermore, we used serum creatinine measurements rather than ICD10 coding to identify AKI, which is a more sensitive approach.

These strengths must be balanced against several limitations. Because data on ethnicity are not typically collected in Australian hospitals, we could not use the ethnicity-adjusted versions of the MDRD II or CKD-EPI equations. A revision of the CKD-EPI equation without race or ethnicity was published in 2021,[24] and further analysis did not change the findings of this study (see Section 3 and Supporting information S1). The ability of our equation to re-classify patients according to the KDIGO criteria was not significantly different from that of MDRD-Fenton equation, which confirms the importance of adjusting for age and gender specific normative values. Although there are few black patients in Australian hospitals, the generalisability of our findings is limited to non-black patients and further research is needed to validate our approach in different ethnic groups as well as in different hospital settings.

Furthermore, the magnitude of serum creatinine change is only one input to any model used to identify AKI. Other inputs should include, for example, the duration of raised serum creatinine levels; the rate of change in serum creatinine; other known comorbidities and risk factors; other data including other lab results, patients' primary admission units, and surgical and radiological procedures performed. The differences in median estimates of baseline serum creatinine with different approaches are small and their clinical importance uncertain. However, depending on the method used to estimate baseline creatinine there can be substantial changes in the classification of patients into AKI and/or different stages of AKI, which in turn are associated with different short-term and long-term risk.

There is currently significant interest in the role of other biomarkers to predict, diagnose, and monitor AKI.[26] These include the combination of insulin-like growth factor binding protein-7 (IGFBP-7) and tissue inhibitor of metalloproteinase 2 (TIMP-2) measured in urine,[27] and equations to estimate glomerular filtration rate which incorporate cystatin C to augment or replace creatinine.[24,28] Some studies have found that incorporating cystatin C into eGFR equations can improve their performance[24]; however cystatin C is more expensive to test than creatinine and it is not measured routinely in many Australian hospitals including our own. Further studies are needed to understand whether estimation of kidney function using these approaches is subject to age bias or other types of bias.

Finally, it is possible that our findings are specific to the population served by our hospital and may not apply to populations admitted to other institutions. We focused on patients who developed AKI over 24 h into their hospital stay, a group of patients with comorbidities associated with a markedly increased risk of intensive care admission and lengthy hospital stays compared to patients with fewer comorbidities. Our study could be externally validated using freely available datasets like MIMIC-IV,[29] which includes electronic health data for patients admitted to the emergency department and intensive care units at Beth Israel Deaconess Medical Center from 2008–2019, with a large, diverse population including patients with (and without) chronic kidney disease, diabetes, and hypertension. Beyond ethnicity, we studied a heterogeneous groups of patients admitted to a typical tertiary hospital in a resource-rich country making it likely that our findings have a substantial degree of external validity to such populations.

5 | CONCLUSION

Conventional approaches to back-estimate baseline serum creatinine using rearranged MDRD-II or CKD-EPI equations with a fixed GFR of 75 ml/min/1.73 m² are biased and inaccurate in patients aged <60 or ≥75. Patients in these age groups together comprise over 68% of patients in our study population, so estimates of baseline serum creatinine must account for changes in glomerular filtration rate with age. Our novel linear equation and an adjusted MDRD equation both improved reclassification of KDIGO AKI stages compared to the MDRD equation with fixed GFR estimates. Our novel equation was simple, less biased, and more accurate than unadjusted equations. It provides an alternative and seemingly superior approach to the estimation of baseline creatinine values in patients at risk of acute kidney injury.

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