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EDITORIAL COMMENTARY

Biologic sex and the estimation of GFR in pediatric and young adult patients with acute kidney injury

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Introduction

Acute kidney injury (AKI) is a common complication among hospitalized pediatric patients [1]. Its recognition is important as AKI is associated with increased mortality and risk of chronic kidney disease (CKD) in children [2]. Especially in neonates, AKI is vastly underrecognized [2, 3]. There were various definitions which influenced the incidence calculations [3], and in 2004, the Acute Dialysis Quality Initiative Group created the Risk, Injury, Failure, Loss, End Stage (RIFLE) criteria [4] An additional modification to the RIFLE criteria has been proposed for pediatric patients in 2007 in order to better classify small children with acute-on-chronic disease, called pRIFLE [5]. In parallel, the Acute Kidney Injury Network (AKIN) criteria were created, which included a > 0.3 mg/dL absolute creatinine increase for the definition [6]. More recently, the Kidney Disease Improving Global Outcomes (KDIGO) classification system integrated the RIFLE, pRIFLE, and AKIN classification systems [7]. AKI is defined as any of the following:

- Increase in SCr by ≥ 0.3 mg/dL (≥ 26.5 µmol/l) within 48 h; or
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume < 0.5 mL/kg/h for 6 h [7].

This definition requires a baseline creatinine; however, this is often not available. There is currently no validated equation for estimating a baseline creatinine in hospitalized children without pre-existing CKD. In that context, we notice the interesting paper by Chloe Braun et al. from the University of Alabama Birmingham School of Medicine which introduces a relatively simple formula for the estimation of the baseline creatinine [8]. This is particularly important in view of the fact that between 27 and 73% of admitted children do not have a known baseline creatinine [8].

The paper by Braun et al.

To determine the baseline creatinine, the authors conducted an analysis of patients aged 0–25 years who were admitted to a single center between 2012 and 2019, and who had at least one pre-admission creatinine prior to the AKI. They included 5,900 hospitalized patients (50.3% male), which is a strong sample size. The sample was biased toward Caucasians (63.9%) They excluded patients younger than 90 days because of the developmental changes of kidney function in the neonatal period. The authors then used a variety of existing formulae for the estimation of the baseline creatinine and developed their own new formulae, which surprisingly were dependent on age only. They proposed two formulae, one simple formula for non-hospital-based estimation, and one improved formula when serum creatinine values are available within 72 h of hospitalization. The simple formula reads:

$$Cr_b = 0.264 \times e^{0.056 \times Age}$$

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The result would be in mg/dL, and Cr_b means baseline creatinine [8]. For conversion to SI units, it should read: $Cr_b = 23.34 \times e^{0.056 \times Age}$; however, this was not written. Consistent reporting for both imperial and SI units would be preferable. This equation performed well with an R^2 of 0.59 in the correlation analysis, while 73.2% of estimated Cr_b were within 30% of true Cr_b values.

This was even better when actual creatinine values within 72 h of admission were available. That formula reads:

$$Cr_b = 0.578 \times [Cr_{min}]^{0.585} \times e^{0.0259 \times Age}$$

The result would be in mg/dL, and Cr_b means baseline creatinine [8]. For conversion to SI units, it should read: $Cr_b = 0.578 \times [Cr_{min}/88.4] \times e^{0.0259 \times Age}$. This equation performed best with an R^2 of 0.75.4 in the correlation analysis, while 86.5% of estimated Cr_b were within 30% of true Cr_b values. The authors' findings were substantially better than published formulae including the original Schwartz equation, while the age-based FAS equation [9] was the best of the existing formulae. A detailed analysis against age showed bias of the FAS equation among very young patients and older adolescents and young adults, and the authors concluded that especially their formula with at least one actual serum creatinine in the first 72 h of admission would have had the best performance. Importantly, the methodology for validation of their formula was appropriate. However, there was no subgroup analysis by sex.

Our sub-analysis by sex

Serum creatinine is very dependent on muscle mass, which differs by sex [10]. Especially starting in puberty, males have significantly higher muscle mass [10]. Therefore, the undersigned believe that the data should have been stratified by sex. We used data of 542 (44.5% female) children with a normal measured GFR to plot the relationship of age and serum creatinine (in SI units, Fig. 1 left) which clearly shows differences by sex. The data were derived from a previous study [11]. When comparing the regression lines, the slopes were significantly different ($F = 5.836$, $p = 0.0031$). If the overall slopes were identical, there is a 0.3098% chance of randomly choosing data points with slopes this different. Figure 1 right shows the simple non-hospital Cr_b formula which falls in the middle of the male and female curves (in black). As such, there is a high probability that the true Cr_b is too low in males, which could potentially overestimate the incidence of AKI. The undersigned encourage the authors to augment their study by including a subgroup analysis by sex.

Possible applications of the study by Braun et al.

Especially in resource-limited countries, where pediatric AKI-associated mortality is disproportionately higher when compared to high-resource countries, but also in developed countries [12], recognition of AKI is very important. The American Society of Nephrology has established a new initiative, AKI!Now, with the goal of promoting excellence in the prevention and treatment of AKI, and the importance of awareness and recognition are stressed [13]. Early recognition and treatment can improve outcomes, while full recovery of kidney function is uncommon, leaving these patients at risk of long-term morbidity and death [14]. The legacy of early nephron loss in pediatric patients is especially troublesome [15].

While artificial intelligence may be a more accurate and promising way to predict AKI [16], Braun et al. offer a

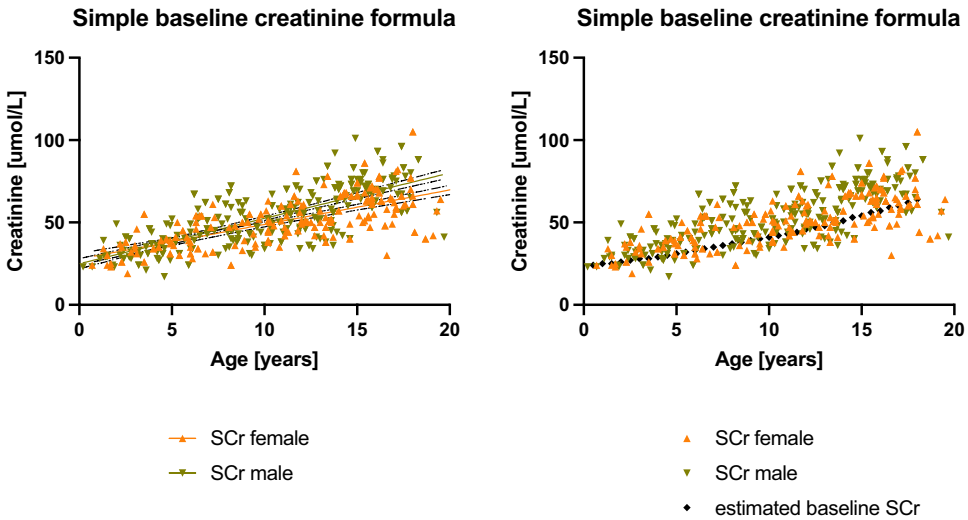

Fig. 1 Serum creatinine by age and sex in SI units and the simple baseline creatinine formula proposed by Braun et al. [8]

simple approach for the baseline creatinine which is needed for the identification of an AKI. Especially when using the non-hospital-based formula by Braun et al. [8], every pediatric patient could be assigned a baseline creatinine if none were available, and an increase of serum creatinine by 0.3 mg/dL could automatically be flagged as AKI. Electronic health records (EHRs) have become an integrated part of medical practice in most clinical settings worldwide [17]. EHRs with rule-based algorithms have been used successfully for prompt AKI detection [17]. We propose to automatically add the non-hospital-based baseline creatinine formula by Braun for any patient aged less than 25 years and to flag the patients if the first creatinine within 72 h has risen more than 0.3 mg/dL. Of note, Braun's formula with at least one creatinine within 72 h after admission was superior, but implementation of that formula in an EHR system would require some artificial intelligence. Also, further research is needed to see if the non-hospital-based formula performance could be improved by adding a sex modifier. However, even the proposed use of the non-hospital-based formula for flagging patients at risk of AKI would be a big advantage, albeit the incidence of AKI in adolescent males may be overestimated. Not only are there substantial economic consequences of AKI (ranging from $11,016 to $42,077 per hospitalization in the USA in the year 2017) [18], but also hospital revenue is affected by under-recognition of AKI.

Conclusion

Despite the lack of stratification by sex, the study by Braun et al. [8] addresses an important knowledge gap with the potential to improve the recognition of AKI among children, adolescents and young adults admitted to the hospital, when no baseline creatinine is available. The non-hospital-based formula is simple and could easily be incorporated into any electronic medical record system. However, this formula could likely be improved by performing a subgroup analysis by sex, which might lead to an even higher precision. We also need to continue to advocate for more widespread use of both cystatin C and creatinine together. More than 20 years after a meta-analysis showed cystatin C to be a superior marker of estimation of GFR [19], availability remains limited, even though it can be measured rapidly for as low as CA$2.40 [20]. We congratulate Braun et al. on this fine study and hope that—after additional analysis—it can be improved further and become standard in the clinical routine for the recognition of AKI among admissions in the pediatric age group. AKI in this age group is poorly documented and underrecognized [21].

Declarations

Conflict of interest The authors declare no competing interests.

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