issue of the *Journal* are crucial to provide data to guide individuals, leaders, and professional society working groups when they face the seemingly daunting task of determining how to increase female mentorship, leadership, and success in the world of academic medicine. ■

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Maryellen C. Antkowiak, M.D.
Polly E. Parsons, M.D.
Renee D. Stapleton, M.D., Ph.D.
Department of Medicine
University of Vermont Larner College of Medicine
Burlington, Vermont

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Identifying the Patient at Risk for Acute Kidney Injury: Pediatric Sepsis Biomarker Risk Model Study

Acute kidney injury (AKI) contributes to adverse outcomes in hospitalized patients across the lifespan, including increased morbidity and mortality, prolonged hospital stays, and higher risk of developing chronic kidney disease (1–4). Identification of patients at risk for the development of AKI would enable closer evaluation of kidney function and implementation of strategies to ideally prevent the development of AKI before onset or lessen its duration and severity. There have been several prior attempts to develop reliable strategies for AKI prediction, including the use of known kidney injury biomarkers (5, 6), attempts at novel candidate biomarker discovery (7), and the renal angina index (RAI) (8, 9). In published reports, the 3-day time point for the development of AKI is chosen because of the poor patient outcomes associated with severe AKI occurring 48 hours after ICU admission and as a point to signify clinically significant AKI. Identification of patients at risk for AKI on Day 0 of illness allows implementation of standardized care bundles promoting renal protection in high-risk patients, which has been shown to reduce AKI severity and associated morbidity (10, 11).

Risk factors for the development of AKI differ depending on patient age, making risk stratification difficult. In neonates, risk factors for developing AKI vary on the basis of gestational age at birth: medication exposures in infants at <28 weeks of gestation and outborn delivery and need for resuscitation in infants from 28 weeks to term gestation (12). Currently, there are no predictive tools for risk stratification of neonates with a high probability

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of developing AKI. In adult and pediatric patients, diagnoses associated with the development of AKI are more closely aligned and include sepsis, nephrotoxic medications, trauma (shock), acute decompensated heart failure, and cardiopulmonary bypass and surgery (13). As a result, scoring systems can be created and statistical models used to predict the subsequent development of AKI. In a population of pediatric patients admitted to the ICU with sepsis, Stanski and colleagues (14), as they report in this issue of the *Journal* (pp. 848–855), used the Pediatric Sepsis Biomarker Risk Model (PERSEVERE-II) to determine if this validated multibiomarker stratification tool for estimating the baseline risk of mortality among children with septic shock (14–16) could predict the development of sepsis-associated severe acute kidney injury (SA-AKI; Kidney Disease: Improving Global Outcomes [KDIGO] stage 2 AKI or higher) on Day 3 after admission. In this report, the PERSEVERE biomarkers C-C chemokine ligand 3, granzyme B, heat shock protein 70 kD 1B, IL-8, and matrix metallopeptidase 8 were measured in serum samples obtained within 24 hours of a septic shock diagnosis. Using the biomarker data and admission platelet counts, the authors classified mortality risk for each patient according to the PERSEVERE-II decision tree as low, intermediate, or high risk. Multivariable logistic regression confirmed that PERSEVERE-II mortality probability was independently associated with increased odds of severe Day 3 SA-AKI, need for renal replacement therapy, and Day 3 renal recovery, with the area under the receiver operating characteristic curve reflecting a sensitivity of 62% and a specificity of 69%.

Because this was not robust enough to inform clinical decision making, the authors then used Classification and Regression Tree methodology to derive a new model estimating the probability of severe Day 3 SA-AKI. In the new model, predictor variables included Day 1 KDIGO AKI stage, PERSEVERE-II mortality probability, and the PERSEVERE biomarkers. The presence of Day 1 KDIGO AKI stage 3 AKI was reasonably predictive of Day 3 SA-AKI with a sensitivity of 85% and a specificity of 81%. For patients with lesser stages of Day 1 KDIGO AKI, the new model significantly improved sensitivity from 62% to 92% and specificity from 69% to 89%, creating a model robust enough to inform clinical decision making.

In contrast to the study by Stanski and colleagues, Basu and colleagues (17) proposed the concept of renal angina, which combines risk factors for AKI with early signs of loss of kidney function (increases in serum creatinine or degrees of fluid accumulation) to stratify patients at risk for subsequent severe AKI (stage 2 or 3 AKI by the KDIGO criteria). The RAI is calculated 12 hours after admission to the ICU (17). Patients are assigned a numeric value based on their risk factors, ICU admission (1), solid organ or stem cell transplant (3), mechanical ventilation/vasoactive support (5), and injury status, which is quantified by change in serum creatinine from baseline and percentage fluid overload with a score between 1 and 8 assigned on the basis of injury severity. The risk score and injury score are multiplied together with a score $\geq$8 indicating the presence of renal angina. The presence of renal angina in this study predicted severe Day 3 AKI with a specificity of 87% versus 70% when compared with serum creatinine alone.

The strength of the PERSEVERE-II biomarker study described above is its sensitivity and specificity. Although the specificity is equivalent to the RAI, the sensitivity for Day 3 severe AKI is 92% versus 67% for RAI. In addition, the positive predictive value in the PERSEVERE-II mortality study was 64% versus 31% for RAI, indicating that the PERSEVERE-II biomarkers may be superior to the RAI for predicting Day 3 severe SA-AKI. Although the number of neonates was small (2.4% of the total cohort) in the PERSEVERE-II study, in the RAI study, all patients were older than 3 months of age; therefore, the PERSEVERE-II biomarker tool may have some applicability to the neonatal population. A limitation of the PERSEVERE-II biomarker tool relative to the RAI is that only patients with sepsis were included, as compared with the RAI study, in which the population was more heterogeneous, including patients with multiple pathologies, making this model more universally applicable. In addition, the PERSEVERE-II biomarkers assayed may not be universally available, as compared with serum creatinine, which was used for the RAI study. The study by Basu and colleagues included data for urine output, making assessment of AKI more reliable than the PERSEVERE-II biomarker study, which included only measurement of serum creatinine and thus may have underestimated the true incidence of AKI.

In summary, identifying patients at risk for AKI provides the opportunity to intervene with preventative strategies that have the potential to improve outcomes. The difference in etiologies between neonatal, pediatric, and adult patients makes universally applicable models difficult to produce. Before the PERSEVERE-II biomarker study, the RAI was the most predictive model for risk of severe AKI on Day 3 of illness. Although the sensitivity, specificity, and positive predictive value of the PERSEVERE-II biomarker study outperform the RAI, future studies are warranted to assess the predictive value of PERSEVERE-II in a more heterogeneous clinical setting. ■

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Jason Gien, M.D.
Department of Pediatrics
University of Colorado
Aurora, Colorado

Danielle Soranno, M.D.
Department of Pediatrics
Department of Bioengineering
and
Department of Medicine
University of Colorado
Aurora, Colorado

ORCID IDs: 0000-0001-8244-9765 (J.G.); 0000-0001-7019-809X (D.S.).

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