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Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children

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Reliable prediction of severe acute kidney injury (AKI) has the potential to optimize treatment. Here we operationalized the empiric concept of renal angina with a renal angina index (RAI) and determined the predictive performance of RAI. This was assessed on admission to the pediatric intensive care unit, for subsequent severe AKI (over 200% rise in serum creatinine) 72 h later (Day-3 AKI). In a multicenter four cohort appraisal (one derivation and three validation), incidence rates for a Day 0 RAI of 8 or more were 15–68% and Day-3 AKI was 13–21%. In all cohorts, Day-3 AKI rates were higher in patients with an RAI of 8 or more with the area under the curve of RAI for predicting Day-3 AKI of 0.74–0.81. An RAI under 8 had high negative predictive values (92–99%) for Day-3 AKI. RAI outperformed traditional markers of pediatric severity of illness (Pediatric Risk of Mortality-II) and AKI risk factors alone for prediction of Day-3 AKI. Additionally, the RAI outperformed all KDIGO stages for prediction of Day-3 AKI. Thus, we operationalized the renal angina concept by deriving and validating the RAI for prediction of subsequent severe AKI. The RAI provides a clinically feasible and applicable methodology to identify critically ill children at risk of severe AKI lasting beyond functional injury. The RAI may potentially reduce capricious AKI biomarker use by identifying patients in whom further testing would be most beneficial.

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Approximately 10% of all children admitted to an intensive care unit (ICU) develop acute kidney injury (AKI), and this rate increases up to 82% with increasing patient severity of illness.[1,2] Increasing AKI severity, characterized by serum creatinine (SCr)- and urine output (UOP)-based stratifications of AKI, is associated with increased mortality in adults[3] and children.[4] Even small increases in SCr (0.3 mg/dl) reflect significant kidney damage and are associated with poor patient outcome.[5,6] The well-recognized limitations of SCr for real-time accurate AKI diagnosis have prevented timely therapeutic interventions.[7] Thus, extensive research efforts have been expended to find earlier, more sensitive biomarkers for AKI.

Several AKI biomarkers have demonstrated promising results for the identification and prediction of AKI in children. However, most have been validated only in the cardiopulmonary bypass (CPB) setting, where demographic homogeneity, lack of comorbidities, and a known onset and duration of ischemic injury provide an ideal biomarker validation environment.[8,9] Demographic heterogeneity likely contributes to the poor discriminatory performance of these biomarkers in non-cardiac pediatric intensive care unit (PICU) patients (area under the curve (AUC) values range from 0.54 to 0.78).[10–13] We previously found that children with persistent AKI at PICU admission (AKI after 48 h) were at the highest risk for requiring renal replacement therapy (RRT).[2] Identifying patients at risk for severe and long-lasting AKI in the PICU, and as importantly, identifying patients unlikely to be at risk, is imperative as risk stratification could allow more judicious AKI biomarker assessment to drive therapeutic intervention, increasing their predictive performance and cost-effectiveness.[14,15] Along these lines, the recent 10th Acute Dialysis Quality Initiative Conference (ADQI-X) issued a directive to use combinations of biomarkers to identify and

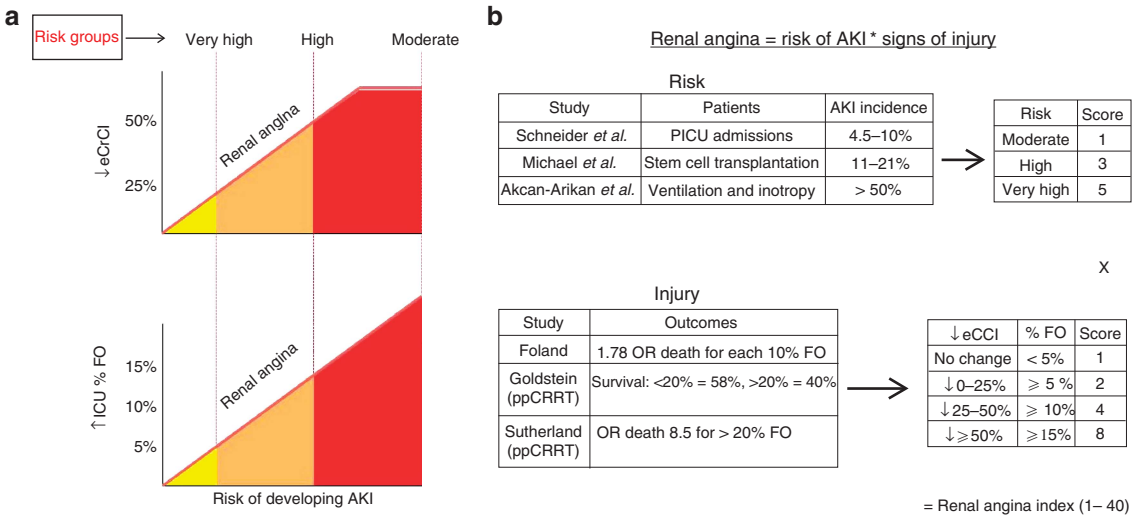

Figure 1 | Renal angina. (**a**) The renal angina construct. The juxtaposed graphs depict risk of acute kidney injury (AKI) versus decrease in estimated creatinine clearance from baseline (↓eCCl) and increase in % intensive care unit (ICU) fluid overload (% ↑ICU FO). There are three risk groups defined for the pediatric ICU population (tranches): very high risk (intubated + presence of at least one vasopressor or inotrope), high risk (history of solid organ or bone marrow transplant), and moderate risk (ICU admission). The construct is created such that less sign of injury (estimated creatinine clearance (eCCl) change or FO change) is required for the higher risk tranches to fulfill renal angina (solid red slope line). (Adapted with permission from Goldstein and Chawla.[26]) (**b**) The renal angina index. On the basis of existing pediatric AKI literature, tiered AKI risk strata were assigned point values for 'risk' and 'signs' of injury. The worse parameter between change in eCCl from baseline and % FO was used to yield an injury score. The full description of the derivation appears in Supplementary A online. The resultant renal angina index score can range from 1 to 40. A cutoff of ⩾8 is used to determine renal angina fulfillment.

differentiate functional AKI ('pre-renal' or 'reversible') from kidney damage (persistent).[16]

The context-based disparity of biomarker efficacy for acute coronary syndrome provides important lessons for the AKI field; troponin demonstrates suboptimal efficacy with capricious, undirected use.[17,18] Although the ability to detect and subsequently expeditiously treat myocardial infarction was augmented with the discovery and incorporation of troponin into the clinical context of cardiac angina, repeated evidence highlights the erosion of troponin performance when measured in patients at low demographic and/or clinical risk of myocardial infarction from coronary disease.[17–23] In addition, independent of troponin, the absence of cardiac angina carries high negative predictive value (NPV) for the diagnosis of a heart attack.[24,25]

To that end, we recently proposed the empiric clinical model of renal angina to identify which critically ill patients would be at the greatest risk of AKI.[26] Using patient demographic factors and early signs of injury, renal angina aims to delineate patients at risk for subsequent severe AKI (AKI beyond the period of functional injury) versus those at low risk (Figure 1a). In the current study, we operationalize renal angina fulfillment by deriving an index (renal angina index: RAI) and, in separate derivation and validation cohorts, test the hypotheses that: (1) renal angina fulfillment using a RAI threshold improves prediction of subsequent severe AKI over severity of illness or risk factors alone and (2) RAI prediction of AKI outperforms currently used clinical thresholds for early signs of kidney injury.

RESULTS

Group characteristics

Demographics for each cohort (C1 ($n = 144$): derivation; C2–C4 ($n = 118$, 108, and 214, respectively): validation) are shown in Table 1. Other than the absence of transplant patients, there were no significant demographic differences between C1 and C3. C4 patients were more severely ill (Pediatric Risk of Mortality II (PRISM-II) score[27]) and had higher use of inotropy and mechanical ventilation than the other cohorts. The overall incidence of the subsequent severe AKI outcome 72–96 h from PICU admission (Day-3 AKI) in the cohorts was 10–20% (C1: 19%, C2: 10.2%, C3: 10.2%, and C4: 13.6%). The optimal RAI cutoff for fulfillment of renal angina (ANG(+), defined by RAI ⩾8) was derived by studying patients from cohort 1 (Supplementary A online).

Derivation cohort (C1)—Cincinnati sepsis #1

Day 0 (PICU admission day) ANG(+) occurred in 51/144 (35%) of patients. Compared with ANG(−) (RAI <8) patients, ANG(+) patients had higher Day-3 AKI rates, longer PICU length of stay (LOS), higher RRT provision, and higher hospital mortality rates (Table 2). Day 0 RAI predicted Day-3 AKI with an AUC of 0.77 (95% confidence interval (CI) = 0.68–0.86). RAI <8 had a high NPV of 92% (95% CI = 85–97%) (Table 3).

Validation cohorts (C2–C4)—Montreal retrospective, prospective, and Cincinnati sepsis #2

Day 0 ANG(+) occurred in 15.3% (C2), 35.2% (C3), and 67.8% (C4) of patients. ANG(+) patients had significantly