The Renal Angina Index Fails to Identify Patients with Subclinical Acute Kidney Injury

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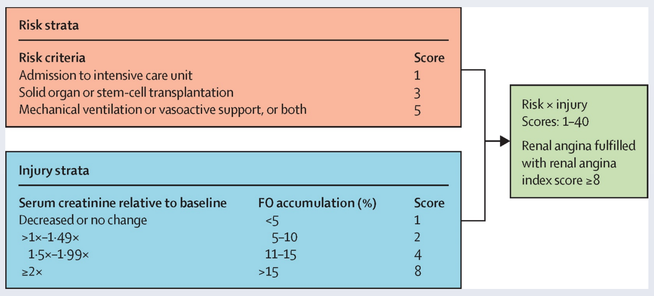
Purpose

- Subclinical acute kidney injury (AKI), a state of tubular injury biomarker positivity in the absence of serum creatinine (SCr) rise, is now a well described entity that has been shown to be common and associated with worse outcomes in critically ill children.
    - Single-center cohort study of PICU patients by Stanski et al. (Journal of Critical Care, 2019) demonstrated:
        - Nearly 20% incidence of subclinical AKI
        - Uniformly worse outcomes for patients with subclinical AKI on admission compared to biomarker negative patients

- However, a knowledge gap exists regarding how to identify high risk patients who should be screened for subclinical AKI with tubular injury biomarkers such as urinary neutrophil gelatinase-associated lipocalin (uNGAL)

- The renal angina index (RAI) is a validated tool calculated 12 hours after PICU admission for predicting AKI at day 3 in critically ill pediatric patients (Basu et al, The Lancet Child & Adol Health, 2018)



Hypothesis

Urinary NGAL testing in patients fulfilling renal angina criteria (RAI+) will allow for identification of patients with subclinical AKI (uNGAL+/SCr-), while simultaneously reducing testing in low-risk patients. These patients with subclinical AKI will have worse outcomes than their biomarker negative counterparts.

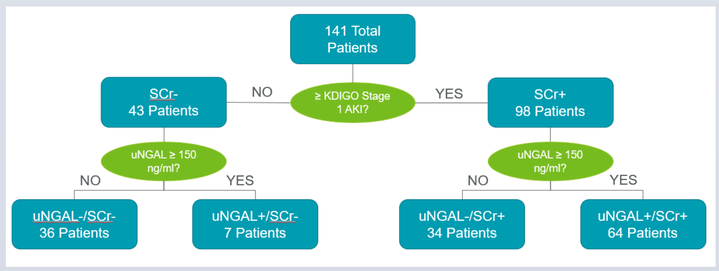
Methods

Design:

- Interim analysis of a single center, prospective, observational cohort of children admitted to the PICU from May 2017 to October 2019 who were RAI+ (RAI ≥ 8) who had uNGAL and SCr samples collected on the day of admission

Definitions:

- Patients were separated into 4 biomarker-based groups based on the presence or absence of elevated uNGAL and SCr on the day of PICU admission



Demographics:

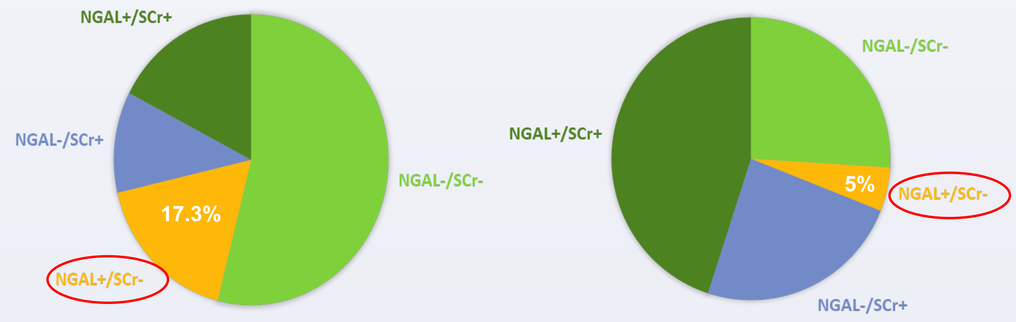
	All	uNGAL-/SCr-	uNGAL+/SCr-	uNGAL-/SCr+	uNGAL+/SCr+	Comparison
N (% total)	141	36 (26)	7 (5)	34 (24)	64 (45)	--
Age, years (IQR)	10.3 (2.1-16)	12.8 (7.2-17.4)	13.6 (7.8-21)	5.8 (2-11.6)	9.3 (1.7-16)	p= 0.058
Male (%)	75 (53)	19 (53)	5 (71)	20 (59)	31 (48)	p= 0.58
Sepsis (%)	51 (36)	5 (14)	2 (29)	10 (29)	34 (53)	p= <0.001
Median No. Comorbidities (IQR)	1 (1-2)	1 (1-2)	2 (1-3)	1 (1-2)	2 (1-2)	p= 0.223
Median No. Nephrotoxins, Day 0 (IQR)	1 (1-2)	1 (1-1)	2 (1-2)	1 (0.75-3)	1 (1-2)	p=0.121
Median No. Nephrotoxins, Day 1-7 (IQR)	1 (1-2)	1 (1-1.8)	2 (1-2)	2 (0-3)	2 (1-2.75)	p=0.121

Outcomes of Interest:

- Severity of Day 3 AKI
    - Any AKI (KDIGO stage 1 or higher)
    - Severe AKI (KDIGO stage 2 or 3)
- Day 3 Fluid Overload (>10%)
- RRT Use
- PICU free days

Results

RAI+ Fails to Detect Subclinical AKI Patients with Expected Frequency:



Subclinical AKI is Associated with Worse Outcomes in RAI+ Patients:

	uNGAL-/SCr-	uNGAL+/SCr-	Comparison uNGAL+ vs. uNGAL-
Any Day 3 AKI (%)	1 (3)	2 (29)	OR 14 (1.1-184, p=0.064)
Severe Day 3 AKI (%)	0 (0)	1 (14)	--
Day 3 FO (%)	6 (17)	5 (71)	OR 12.5 (1.9-80, p=0.008)
RRT Use (%)	1 (3)	0 (0)	--
Median ICU Free Days (IQR)	21 (20-24)	17 (0-24)	p= 0.232

RAI+ Patients with Subclinical AKI Receive More Nephrotoxins:

	uNGAL-/SCr-	uNGAL+/SCr-	Comparison uNGAL+ vs. uNGAL-
Median No. of Nephrotoxins Received, Day 0 (IQR)	1 (1-1)	2 (1-3)	*p*= 0.010
Median No. of Nephrotoxins Received, Day 1-7 (IQR)	1 (1-1.8)	2 (1-2)	*p*= 0.026

Conclusions and Future Directions

Conclusions:

- Subclinical AKI appears to be associated with worse outcomes in patients fulfilling renal angina criteria

- However, the incidence of subclinical AKI in this RAI+ cohort is lower than expected, suggesting that the RAI is an inadequate screening tool for identifying these patients

- The receipt of nephrotoxins may play a role in the development of subclinical AKI, and should be considered when determining who to screen with tubular injury biomarkers such as uNGAL

Future Directions:

- Plan to continue enrollment in this study to goal of 250 patients

- Further study is warranted to determine who may benefit from testing for subclinical AKI

- The potential role of nephrotoxins in the development of subclinical AKI needs to be explored further