

Association between Urine Neutrophil Gelatinase-associated Lipocalin and Proteinuria in Non-Cardiac Postoperative Neonates

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Background

- Current definitions for acute kidney injury (AKI) use only biomarkers of functional renal impairment
- Markers of direct tubular nephron injury can help subclassify AKI into a more homogenous population for targeted treatment interventions
- Urine Neutrophil Gelatinase Associated Lipocalin (uNGAL) is a marker of tubular nephron injury and has previously been associated with higher urine microalbumin concentrations in infants with a hemodynamically significant patent ductus arteriosus (PDA)
- We have previously demonstrated that uNGAL ≥ 150 ng/dL is associated with neonatal AKI
- We aimed to understand the relationship between urine protein loss and urine microalbumin loss and early postoperative elevated uNGAL following non-cardiac procedures

Methods

Inclusion criteria

- Level IV NICU
- <1 year corrected gestational
- Needing a non-cardiac procedure

Exclusion criteria

- Fetal identification of CAKUT with anhydramnios/oligohydramnios
- Current recipient of ECMO or ECMO in the last 7 days
- Gastric tube placement alone

Sample Collection

- Urine was collected preoperative and at approximately 12, 24, 36, 48, 72 and 96 hours postoperative and stored for up to 72 hours prior to processing
- Batch analysis was performed for uNGAL (The uNGAL test™, Bioporto, Denmark), urine creatinine, urine protein, and urine microalbumin (automated chemistry analyzer)
- Minimum and maximum concentrations were recorded at the set corresponding boundary value

Definitions & Outcomes:

- Early elevated uNGAL: uNGAL ≥ 150 ng/mL (within the first 48 hours after the procedure)
- UPC- urine protein to urine creatinine (mg/mg); proteinuria defined as ≥ 0.8 mg/mg
- UMC- urine microalbumin to urine creatinine (mg/g); microalbuminuria defined as ≥ 20 mg/g
- Fluid balance: calculated by both weight-based and cumulative intake-output definitions
- Subgroups for comparison were defined a priori as a uNGAL of ≥ 150 ng/mL postoperative to 48 hours versus those that < 150 ng/mL to 48 hours postoperative
- Subgroups were compared using mean (SD) or median [IQR] for numerical data and N% for categorical data
- Comparisons for non-varying characteristics related to patient or procedural data were performed using Chi-square analysis for categorical variables or the Wilcoxon rank sum test for continuous variables
- Generalized additive mixed models (GAMM) where a random intercept for each procedure was included was used to assess trends of UPC and UMC over time
- R statistical software (version 4.0.4, The R Foundation for Statistical Computing) was used for GAMM and AUC-ROC analysis (packages “mgcv” version 1.8-33 and “pROC”)

Results

- 120 surgical procedures from 91 enrolled subjects
- 39 procedures had early elevated uNGAL with preoperative and intraoperative characteristics described in Table 1
- Temporal concentration changes between subgroups for uNGAL using GAMM are described in Figure 1
- Subjects with postoperative early elevated uNGAL were more likely to experience a lower median serum albumin concentration (uNGAL < 150 ng/mL: 2.7 g/dL [2.4, 3.1] vs. ≥ 150 ng/mL: 2.3 ng/mL [2.1, 2.6])
- There were 507 samples (83%) with proteinuria (≥ 0.8 mg/mg) and near complete microalbuminuria (99.8% of samples)
- UMC and UPC were compared using box plot with significant differences in the median concentrations perioperatively (Figure 2)
- UPC: uNGAL ≥ 150 ng/mL subgroup 2.2 mg/mg [IQR: 1.4, 3.4] vs. 1.3 mg/mg [IQR: 0.9, 2.0], p=0.0009
- UMC: elevated uNGAL ≥ 150 ng/mL subgroup 251 mg/g [132, 757] vs. 168 mg/g [109, 295], p=0.0012
- Trends overtime between subgroups for UPC, and UMC were plotted using GAMM (Figures 3 & 4)

Table 1. Characteristics between uNGAL subgroups perioperatively

Characteristics	Total Number N=120	uNGAL concentration (ng/mL)		p value
		< 150 N=81	≥ 150 N=39	
Demographic & Preoperative				
Race (%) (Not included: Asian, Multiracial n=2)				0.03
Black	29 (24%)	15 (19%)	14 (36%)	
White	78 (65%)	59 (73%)	19 (48%)	
Unknown/Not disclosed	11 (9%)	5 (6%)	6 (15%)	
Ethnicity (%) (Not included: Hispanic n=2)				0.05
Not Hispanic or Latino	111 (93%)	77 (95%)	34 (87%)	
Unknown/Not disclosed	7 (6%)	2 (2%)	5 (13%)	
Past medical history of AKI (%)	26 (22%)	12 (15%)	14 (36%)	0.02
Anchor Weight (kg) [IQR]	3.3 [2.7, 4.3]	3.4 [2.8, 4.4]	2.9 [2.4, 4.1]	0.04
Serum Albumin (g/dL) (%)	3.0 [2.6, 3.3]	3.1 [2.8, 3.3]	2.6 [2.5, 3.1]	0.003
Procedural				
Emergent Procedure (%)	10 (8%)	2 (2%)	8 (21%)	0.002
Surgical Approach (%) (Not included: Thoracotomy, Thoracoscopy, or >1 (n=10))				0.002
Laparotomy	52 (43%)	24 (30%)	28 (72%)	
Laparoscopy	29 (24%)	25 (31%)	4 (10%)	
Neurosurgical	7 (6%)	6 (7%)	1 (3%)	
Other	22 (18%)	18 (22%)	4 (10%)	
EBL (mL) [IQR]	2 [0,11]	1 [0, 6]	10 [0, 30]	0.01
5% Albumin Recipient (%)	58 (48%)	32 (40%)	26 (67%)	0.009
Platelet Transfusion (%)	24 (20%)	8 (10%)	16 (41%)	0.001

Figure 1. Urine NGAL concentration changes perioperative

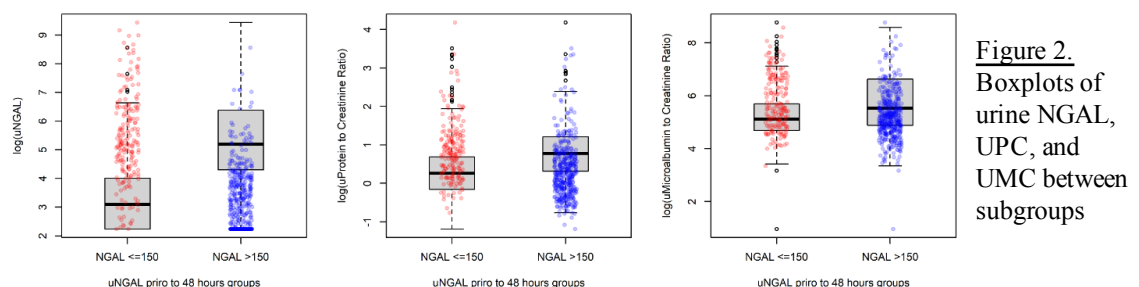
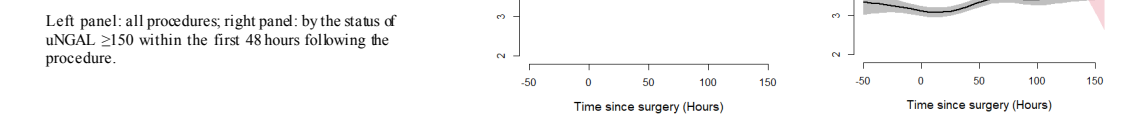


Figure 3. Change in urine protein to urine creatinine (mg/mg) over time perioperatively

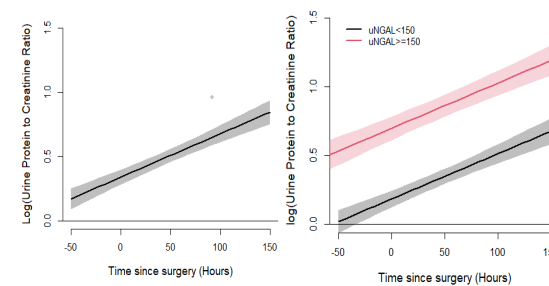
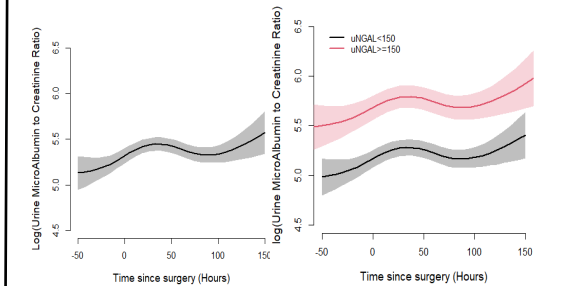


Figure 4. Change in urine microalbumin to urine creatinine (mg/g) over time perioperatively



Conclusions

- Proteinuria and Microalbuminuria are common following non-cardiac procedures
- UPC and UMC ratios are higher in those who demonstrate an elevated uNGAL ≥ 150 ng/mL following surgery before 48 hours
- Future understanding of relationship of proteinuria and microalbuminuria cutoffs that correlate to ventilator free days and patient entered outcomes are needed



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