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Association between Elevated Urine Neutrophil Gelatinase-Associated Lipocalin and Postoperative Acute Kidney Injury in Neonates

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Abstract

Objective: To examine the incidence of postoperative neonatal acute kidney injury (AKI) following general surgical procedures and to test the hypothesis that postoperative urine neutrophil gelatinase-associated lipocalin (uNGAL) concentrations predict AKI. The secondary objective was to evaluate for an association between AKI and hospital mortality.

Study design: Prospective observational study of infants undergoing abdominal and thoracic surgical procedures in the neonatal intensive care unit from October 2018 - March 2020. The primary outcome was incidence of neonatal AKI (defined by the neonatal modified Kidney Diseases Improving Global Outcomes criteria) following each procedure to postoperative day 5. Severe AKI was defined as Stage 2 or 3 AKI. Urine samples were obtained pre- and postoperatively at 6 time points to evaluate for levels of uNGAL. Secondary outcomes were in-hospital mortality and length of stay.

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Results: Subjects (n=141) underwent a total of 192 general surgical procedures during the study period. Neonatal AKI and severe AKI occurred following 36 (18%) and 15 (8%) procedures (n=33 subjects). Percent change of uNGAL from 24-hours preoperatively to 24-hours postoperatively was greater in subjects with neonatal AKI (190.2% [IQR: 0.0, 1666.7%] vs 0.7% [IQR: -31.2%,140.2%], $P = .0374$). The strongest association of uNGAL and AKI occurred at 24 hours postoperatively (AUC-ROC of 0.81, 95% CI: 0.72, 0.89). Increased mortality risk was observed in subjects with *any* postoperative AKI (aOR 11.1 95%CI 2.0, 62.8 $p=0.0063$) and severe AKI (aOR 13.8; 95%CI 3.0, 63.1, $p=0.0007$).

Conclusion: Elevation in uNGAL 24-hours postoperative was associated with AKI. Neonates with postoperative AKI had increased mortality.

Acute kidney injury (AKI) is associated with increased risk for morbidity, mortality and progression to chronic kidney disease in critically-ill neonates.(1–7) However, the current definition of neonatal AKI, the neonatal modified Kidney Diseases: Improving Global outcomes (nKDIGO) criteria, utilizes functional biomarkers, serum creatinine (SCr) and urine output (UOP), which have well known limitations and are imperfect for AKI detection in neonates.(1, 2, 8–10) Consequently, validation of biomarkers to detect neonatal AKI remains an unmet need. (1, 11, 12)

Urine neutrophil gelatinase-associated lipocalin (uNGAL) is a candidate biomarker for detecting nephron insult earlier, improving accuracy and timing of diagnosis of neonatal AKI.(9, 13–16) Urine NGAL is released by the kidney tubular epithelial cells in response to injury and is the most extensively studied kidney structural biomarker in children.(17) Specifically, in neonates undergoing postoperative cardiac surgery for congenital heart disease, elevations in uNGAL concentration and uNGAL kinetics predict severity of postoperative AKI.(9, 18–22) Following cardiopulmonary bypass, uNGAL concentrations > 150 ng/ml are associated with a higher postoperative dialysis rate, longer intensive care unit stay, and increased mortality.(23)

Research related to the association between *non*-cardiac surgeries and neonatal AKI is scarce.(1, 7, 24–35) Recent single center retrospective data suggest an association between AKI and general abdominal surgeries, however only one study demonstrated increased risk for mortality and neither evaluated urine biomarkers.(36, 37)

We aimed to address this knowledge gap by evaluating the relationship between postoperative uNGAL concentrations and AKI development in neonates undergoing general abdominal and thoracic surgical intervention. We hypothesized that elevated uNGAL concentrations postoperatively would be associated with postoperative AKI and that individual percent change of uNGAL concentrations from pre- to postoperative would predict development of AKI.

Methods

This prospective cohort study enrolled neonates admitted to the Cincinnati Children's Hospital Medical Center neonatal intensive care unit (NICU) between October 2018 and March 2020. Infants eligible were undergoing a general abdominal or thoracic surgical

procedure and were <6 months corrected gestational age (CGA). Exclusion criteria were: gastrostomy tube placement alone, current recipient of extracorporeal membrane oxygenation (ECMO), ECMO within 7 days, or previous prenatal consultation for congenital anomaly of the kidney and urinary tract. The study was approved by the Cincinnati Children's Institutional Review Board. In most cases, informed parental consent was obtained prior to surgery; for emergent surgical interventions, the IRB permitted consent up to 12 hours following the procedure. Infants were prospectively followed from 24 hours prior to their first enrolled procedure to NICU discharge or death, whichever came first.

Definition of Outcomes

The primary outcome was postoperative AKI. AKI and associated staging was defined by the nKDIGO AKI SCr and UOP definitions (Table I; available at www.jpeds.com).^(1, 8) Additionally, UOP in the first 24 hours of life was excluded from analysis secondary to normal physiologic variance, and post baseline SCr was required to be above 0.5 mg/dL to be defined as AKI.^(7, 38) Postoperative AKI was defined as a continuation or worsening stage of preoperative AKI (AKI occurring 7 days prior to the procedure), or occurrence of AKI following the procedure to postoperative day (POD) 5. Subjects with only one SCr measurement prior to POD 5, which did not meet AKI criteria, were assumed to not have AKI. AKI stage in subjects who met both SCr and UOP criteria was defined as maximum AKI stage reached. Secondary outcomes included severe postoperative AKI (stage 2 or 3 using either criterion), length of hospital stay, and mortality, defined as death prior to hospital discharge.

Data and Sample Collection

Subject and procedure data were recorded from the electronic health record. Medical history, surgical diagnosis, surgical approach, nephrotoxic medication exposure, and anesthesia time for each procedure were recorded.⁽³⁹⁾ Routine vs. emergent surgery (procedure in which pathophysiology necessitated surgical intervention within 24 hours to improve chance of survival) was recorded. Day of surgical intervention was classified as POD 0. Urine samples were obtained preoperatively and at approximately 12, 24, 36, 48, 72, and 96 hours postoperatively, with exact times of collection recorded. Samples were collected by indwelling bladder catheter if in place for clinical care, or by cotton. Urine output was recorded every 2 hours in subjects who had a bladder catheter or every 4 hours with diaper changes. Serum creatinine values were collected at the discretion of the clinical team. In subjects that underwent a subsequent procedure past POD 5, any changes to medical history and perioperative data were documented and urine samples were again obtained pre- and postoperatively according to the methods.

Sample Processing

Urine was stored in a unit research refrigerator at 4°C for 48 hours with extension to 72 hours to allow for processing during the weekday. Published data confirms that storage of urine at 4°C up to 48 hours prior to processing does not affect uNGAL concentrations.⁽⁴⁰⁾ Our laboratory has validated that storage of up to 72 hours prior to processing does not affect uNGAL concentrations (unpublished data). Samples from consented subjects

were spun at 3500 RPM for 15 minutes, aliquoted, and stored at -70°C until batched analysis. Urine NGAL measurement was performed by the Cincinnati Children's Biomarker Laboratory using The NGAL Test™ (BioPorto Diagnostics, Denmark). Urine Creatinine measurements (uCr) were obtained via enzymatic creatinine test on a Siemens Dimension RXL Max clinical chemistry system. Results were not available to the clinical team.

Statistical Analyses

A consecutive sample of subjects was identified from anticipated surgical cases meeting inclusion and exclusion criteria over 2 years. Demographic data, such as GA, sex, and kidney anomalies were examined at the subject level and procedural level. Past medical history of AKI and perioperative data were recorded. Following each procedure, comparisons between subjects with and without AKI were performed using univariate mixed effect models where subjects were used as a random effect to account for multiple procedures per subject. Demographic and perioperative characteristics were summarized using mean (standard deviation) or median [interquartile range (IQR)] for numerical variables and N (%) for categorical variables. Comparisons for non-varying characteristics used exact Chi-square analysis for categorical variables, and Wilcoxon rank test for continuous variables. Urine NGAL was log transformed due to skewed distribution prior to assessment of the longitudinal trajectory by Generalized Additive Mixed Models (GAMM). Performance of uNGAL and uNGAL/uCr ratios at specific time points to predict post-surgical AKI was assessed using sensitivities, specificities, and area under the receiver operator curves (AUC-ROC). Mortality and length of stay (LOS) was examined for the subject data. Logistic regression was used to assess mortality and LOS at the subject level. Characteristics with a $p < 0.10$ in bivariate analysis were considered for the final logistical model, and variables included were restricted by the degrees of freedom. Adjusted parameter estimates or odds ratios (aOR) were calculated with 95% confidence. SAS Statistical Software (version 9.4, SAS Institute, Cary NC) was used for descriptive statistics and mixed model analysis; R statistical software (version 3.4.3, The R Foundation for Statistical Computing) was used for GAMM and AUC-ROC analysis (package "mgcv" version 1.8–17 and "pROC").(41–43) A p value of < 0.05 was considered significant.

Results

Participants

Of the 166 subjects who met eligibility criteria, 143 neonates were enrolled between October 2018 and March 2020 (Figure 1; available at www.jpeds.com). Two subjects were additionally excluded: one subject never underwent surgical intervention and one subject recovered in unit other than the NICU. Median GA of enrolled subjects was 35 weeks [IQR: 30,37]. Subjects were predominately White ($n=119/141$, 84%) and male ($n=78/141$, 55%), which is reflective of the eligible Cincinnati Children's NICU population. Twenty-two subjects had identified kidney anomalies on ultrasound. Of the 141 subjects, 33 underwent more than one intervention; median number of interventions per subject was 2 procedures [IQR:2–3]. A total of 192 procedures with 1,070 urine samples were analyzed.

Postoperative AKI (Primary Outcome)

The AKI incidence following procedures was 19% (36/192, 95%CI: 0.135–0.250, $p<0.0001$) which occurred in 33 subjects. In the 3 subjects who experienced a second occurrence of postoperative AKI following a subsequent procedure, timing from previous procedure ranged 24–61 days. Twenty-one occurrences were stage 1, ten stage 2, and five stage 3. Twenty-three occurrences were defined by UOP alone, eight by SCr alone, and five by both UOP and SCr (Figure 2; available at www.jpeds.com). AKI incidence did not change over the 2-year course of study. Median time to postoperative AKI was 21.5 hours [IQR:15.6, 30.5] and to maximum stage was 27.3 hours [IQR: 18.1, 43.4]. Preoperative AKI was present in 28% (10/36) of procedures where postoperative AKI developed (Figure 2).

Factors Associated with Postoperative AKI

Demographic, pre-, intra- and post-procedure characteristics are listed in Table 2. Risk factors for postoperative AKI included: previous AKI history (42% vs. 20%, $p=0.025$), preoperative nephrotoxic medication exposure (37% vs. 19%, $p=0.032$), younger corrected GA at time of intervention (38 weeks [IQR:34, 41] vs. 40 weeks [IQR:36, 45]), and emergent procedure (64% vs. 30%, $p<0.001$). Subjects with postoperative AKI had more frequent SCr screening post-procedure (5 [IQR:4,8] vs. 3 [IQR: 2,4], $p<0.0001$). Duration of nephrotoxic medication exposure to POD 5 was longer in subjects who developed AKI (3 days [2, 4] vs. 2 days [1,3], $p=0.030$).

Association of AKI with Urine NGAL

Median time from urine sample collection to processing was 31.2 hours (IQR: 15.7, 44.5) with 80% processed at <48 hours. Processing times between subgroups did not differ (*AKI*: 32.2 (IQR: 15.7, 45.6), *No AKI*: 331.0(IQR: 15.7, 44.3), $p=0.55$). There was no difference in preoperative uNGAL concentrations between AKI and no AKI subgroups (Table 3). Urine NGAL concentrations were higher at all postoperative time points for subjects with postoperative AKI irrespective of inclusion or exclusion of subjects with preoperative AKI (Table 3) and were similar when assessed to uCr. Urine NGAL concentrations at 24 hours had the best performance to predict AKI (*procedures with preoperative AKI included*: AUC-ROC 0.81; 95%CI: 0.72, 0.89; cutoff: 144 ng/mL; specificity 74%; sensitivity 81%; *excluded*: AUC-ROC 0.79; 95% CI: 0.70, 0.89; cutoff: 81 ng/mL, specificity 63%; sensitivity 91%) (Figure 3) and was similar when assessed by uNGAL/uCr ratios (*procedures with preoperative AKI included*: AUC-ROC 0.80; 95%CI:0.71, 0.89; cutoff: 192 ng/g; specificity 82%; sensitivity 71%; *excluded*: AUC-ROC 0.77; 95%CI: 0.67,0.88; cutoff: 192 ng/mL, specificity 82%; sensitivity 65%). The percent change in uNGAL concentrations from pre- to 24 hours postoperative was greater in subjects with postoperative AKI (190.2% [IQR: 0.0, 1666.7] vs. 0.7% [IQR: -31.2, 140.2], $p=0.037$). The difference increased when subjects with preoperative AKI were excluded (529.8% [IQR: 5.9, 2097.1] vs. 1.2% [IQR: -30.8, 148], $p=0.017$).

We assessed the temporal relationship between uNGAL increase and AKI diagnosis. Subjects with preoperative AKI or without a uNGAL obtained prior to meeting AKI criteria were excluded ($n=22$). Of the 14 remaining subjects, 12 (86%) had elevated uNGAL concentrations (>81 ng/mL) prior to meeting AKI criteria.

Postoperative Chronological Trends of uNGAL Concentrations

The predicted trajectories of log-transformed uNGAL concentration over time were modeled and plotted between AKI and no AKI groups using General Additive Mixed Models (GAMM) (Figure 4, A). Log-transformed uNGAL concentrations were similar before operation. Postoperative uNGAL concentrations were higher in subjects that developed AKI. Peak difference in uNGAL concentration between the two groups was seen at 24–48 hours postoperatively. To further assess impact of illness acuity on uNGAL variation, emergent and routine procedures were analyzed separately. Preoperative uNGAL concentrations for emergent procedures were higher than those for routine procedures, but difference decreased post procedure (Figure 4, B). To further clarify emergent vs. routine procedure uNGAL temporal trends, trajectories of AKI and no AKI groups were plotted by procedure sub-type (Figure 4, C and D). Despite similar preoperative uNGAL concentrations prior to emergent procedures, subjects who experienced postoperative AKI demonstrated a uNGAL peak postoperatively and those that did not have AKI displayed a steady decline (Figure 4, C).

Two subjects had preoperative AKI without continuation postoperatively. In these subjects, preoperative uNGAL concentrations were above the 3rd quartile for all procedures (29.7 ng/dL [IQR: 9.38,104.0]; subject A: pre-procedure uNGAL: 135 ng/mL; subject B: pre-procedure uNGAL: 1130 ng/mL). Following both procedures, uNGAL remained low (A: range 9.38–48.2 ng/mL) or decreased consistently from 12 hour to 96-hour concentration (B: 2970 ng/mL to 170 ng/mL).an

Association of AKI with Secondary Outcomes

Ten subjects (7%) died prior to NICU discharge with 8 subjects experiencing at least one postoperative AKI event. Subjects with any stage postoperative AKI and severe AKI had increased NICU mortality risk (*any AKI*: OR 17.0; 95%CI: 3.4, 84.8; $p=0.0006$; *severe AKI*: OR: 20.3; 95%CI 4.8, 85.4; $p=0.0001$) which remained when adjusted for birth GA, any emergent procedure, and undergoing multiple procedures (*any AKI*: aOR 11.1, 95%CI: 2.0, 62.8; $p=0.0063$; *severe AKI*: aOR 13.8, 95%CI: 3.0, 63.1; $p=0.0007$). In the 2 subjects without AKI post-procedure and death as an outcome, there was additionally no past medical history of AKI during their hospitalization and both subjects had SCr checked daily postoperatively. Length of stay was not different between AKI and no AKI groups after controlling for birth GA, any emergent procedure, and multiple procedures ($\beta: 5.01$, *standard error*: 11.21, $p=0.79$). Only one subject, who had AKI and death as an outcome, received renal replacement therapy.

Association of uNGAL with Secondary Outcomes

Excluding subjects with pre- and postoperative AKI, uNGAL was elevated at 24 hours following 37 procedures. Peak uNGAL concentration in the two subjects with death as an outcome without AKI occurred at 36 hours respectively (147 ng/dL and 303 ng/dL). An increased hospital length of stay between subjects with any 24-hour elevated uNGAL (>144 ng/mL) postoperatively and no elevated uNGAL (<144 ng/mL) irrespective of AKI criteria was observed in the univariable model ($\beta: 29.6$; *standard error*: 13.7, $p: 0.0329$), but this effect disappeared after controlling for birth gestational age, any emergent procedure and subjects who underwent multiple procedures ($\beta: -0.96$; *standard error*: 11.9, $p: 0.94$).

Discussion

This large prospective cohort study supports previous work that neonates undergoing surgical procedures are at risk for AKI.(7, 33, 37) At 24-hours postoperatively, uNGAL had a strong prediction performance for AKI using a cutoff of 144 ng/mL, demonstrating potential as a useful tool for detecting kidney damage. Sensitivity at 24 hours improved to 91% with a cutoff concentration of 81 ng/mL when subjects with preoperative AKI were additionally excluded (Figure 3), and findings were similar when assessed relative to urine creatinine. These findings further validate previously reported associations between uNGAL and neonatal AKI.(18, 19, 25, 44–49)

Our findings also demonstrated that preoperative uNGAL concentrations *alone* cannot predict postoperative AKI. However, elevations in uNGAL concentrations post procedure were observed in subjects that developed AKI compared with uniformly low uNGAL concentrations in those that did not (Figure 4). Thus, examining percent change in uNGAL from pre- to 24-hours post procedure may also prove a useful clinical tool. Further analysis into thresholds of percent change to prompt serial SCr monitoring are warranted.

It has been proposed that elevation in uNGAL without clinical AKI (functional loss) represents early kidney injury and thus should be included in the clinical definition of AKI. (50–53) In our cohort of subjects, uNGAL was elevated at 24 hours (>144 ng/mL) following 37 procedures without any evidence of functional loss (pre- or postoperative AKI). Our cohort strengthens the need for analysis of uNGAL in a large sample size of neonates against outcomes such as mortality, length of stay and chronic kidney disease.

Our study expands what is known about postoperative AKI and highlights the challenges of defining AKI in neonates. In contrast to the using Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) nKDIGO AKI definition, we utilized the 2014 nKDIGO definition of AKI for UOP criteria due to the prospective nature of this study. We felt that neonates with oliguria or anuria followed by polyuria may not qualify for the 2017 definition and become excluded despite having significant renal injury. In our cohort, 66% subjects met criteria for AKI by UOP *alone*. At 36 hours post procedure, 40% of subjects had a foley in place for clinical care and this may have contributed to a higher ascertainment of UOP defined AKI. This finding is supported by the Assessment of Worldwide Acute Kidney Injury, Renal angina and Epidemiology and AWAKEN studies where plasma creatinine levels alone failed to identify 2/3 of children and 1/3 of neonates, respectively.(1, 54)

Eight occurrences of AKI were defined by SCr *alone*. Three subjects had preoperative AKI, which likely triggered providers to closely monitor with serial SCr postoperatively. However, five subjects did not have pre-operative AKI and thus would not regularly have serial SCr followed. The fact that over half of these subjects had elevated SCr meeting AKI criteria postoperatively, despite normal SCr preoperatively, further supports the need for serial SCr monitoring following at-risk events. Yet, clinical adoption of routine SCr screening continues remains challenging in neonatology. Iatrogenic anemia in very low birth weight infants, and pain or difficulty from repeated vascular access attempts, have

prompted clinicians to carefully evaluate clinical utility and risk/benefit of each blood draw in neonates. Point-of-care testing using minimal serum sample is commonly used in our NICU for blood gases and includes electrolytes and hemoglobin but excludes serum creatinine. Inclusion of SCr on point-of-care testing on blood gas sampling would have increased ability to observe SCr trends on 23 subject days, potentially increasing AKI ascertainment based on SCr. Thus, we must continue to define timing and risk factors, in addition to finding alternative methods, for accurate AKI diagnosis.(50, 55)

Our study also prospectively assesses AKI in neonates with gastroschisis, omphalocele, or tracheoesophageal fistula and/or esophageal atresia, each of which could increase AKI risk from hypovolemia and/or increased abdominal pressure following surgery. This further builds upon the retrospective reviews of risk-factors and outcomes of AKI following neonatal general surgical procedures.(36, 37) Furthermore, we examined subjects receiving emergent and routine procedures to determine if only subjects undergoing emergent procedures were at increased risk for AKI secondary to underlying pathophysiology.

Higher AKI rates observed in subjects undergoing emergent procedures is expected as the acuity of subjects requiring such interventions have previously demonstrated high-risk for AKI (NEC with or without bowel perforation, abdominal compartment syndrome).(6, 56, 57) However, inclusion of infants undergoing routine procedures is important, as AKI occurred after 12% of non-emergent surgeries, suggesting infants should be assessed for AKI development after routine surgical intervention. Our observations that AKI and severe AKI were associated with high risk of NICU mortality is consistent with the existing neonatal AKI literature.(1, 4, 20)

Our study has several strengths. It is a large prospective cohort of neonates undergoing non-cardiac surgical intervention, an understudied population. Rates of AKI in this population are consistent with ancillary studies from the AWAKEN cohort and other studies that have identified infants undergoing surgery as being at risk for AKI.(6, 7, 33, 34, 37, 56, 58, 59) Additionally, because patients undergoing thoracic and abdominal surgery require close monitoring, a large proportion of our cohort had indwelling urinary catheters. This allowed for regularly quantified UOP, improved reliability in assessing for AKI, and less cumbersome and more accurate sample collection. We also obtained uNGAL preoperatively and assessed for preoperative AKI to account for potential influences prior to surgical operations and thus adjust our model. We additionally recorded collection method of each sample as collection methods for urine biomarkers via cotton have demonstrated an increase in observed variability.(60) This allowed us to conclude that method of collection did not impact the overall significance of our results.

Despite these strengths, various limitations must be considered. First, although the number of procedures was large, we had a modest (18%) rate of AKI, and thus the sample size was too small to risk stratify across gestational ages which are a known contributor to uNGAL variability.(19) This limited the number of confounders included in multivariable analysis for associations with mortality. Reliance on SCr obtained by routine clinical care may have negatively affected SCr AKI ascertainment.

Furthermore, 67 of the 192 procedures occurred in the first week of life, with 38 of those occurring in the first 24 hours following birth. Early AKI diagnosis using SCr and UOP has several additional known limitations and infants may have had UOP AKI in the first 24 hours that was attributed to normal newborn physiology.(7, 61) Finally, maternal data were not collected and thus infants who underwent surgical intervention in the first 24 hours of life may have had additional unaccounted associations from maternal influences.

This single center study demonstrated that elevated uNGAL at 24-hours post general thoracic or abdominal procedure was associated with AKI in neonates. Additionally, this study displayed that preoperative NGAL was not associated with postoperative AKI, however, change from baseline may prove a useful clinical tool. The added benefit of uNGAL collection being less invasive than serum blood draws offers opportunity to postoperatively monitor for AKI while potentially reducing risk of iatrogenic anemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

AKI	Acute Kidney Injury
uNGAL	Urine Neutrophil Gelatinase-Associated Lipocalin
nKDIGO	Neonatal Modified Kidney Diseases Improving Global Outcomes
SCr	Serum Creatinine
UOP	Urine Output
IQR	Interquartile ranges
uCr	Urine Creatinine
LOS	Length of Stay
AUC-ROC	Area Under the Receiver Operating Characteristics

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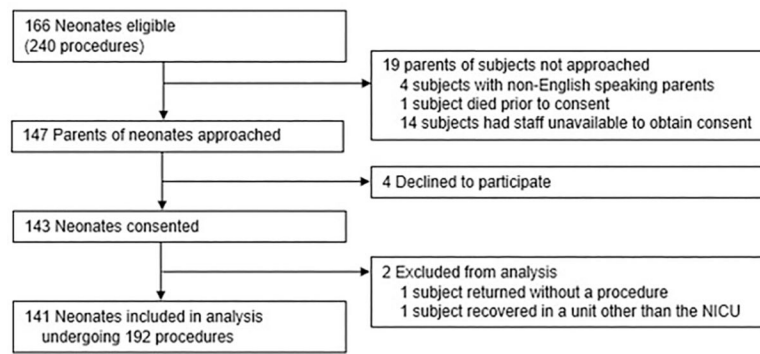


Figure 1, online.
STROBE diagram of the study cohort
Abbreviation: Neonatal Intensive Care Unit, NICU

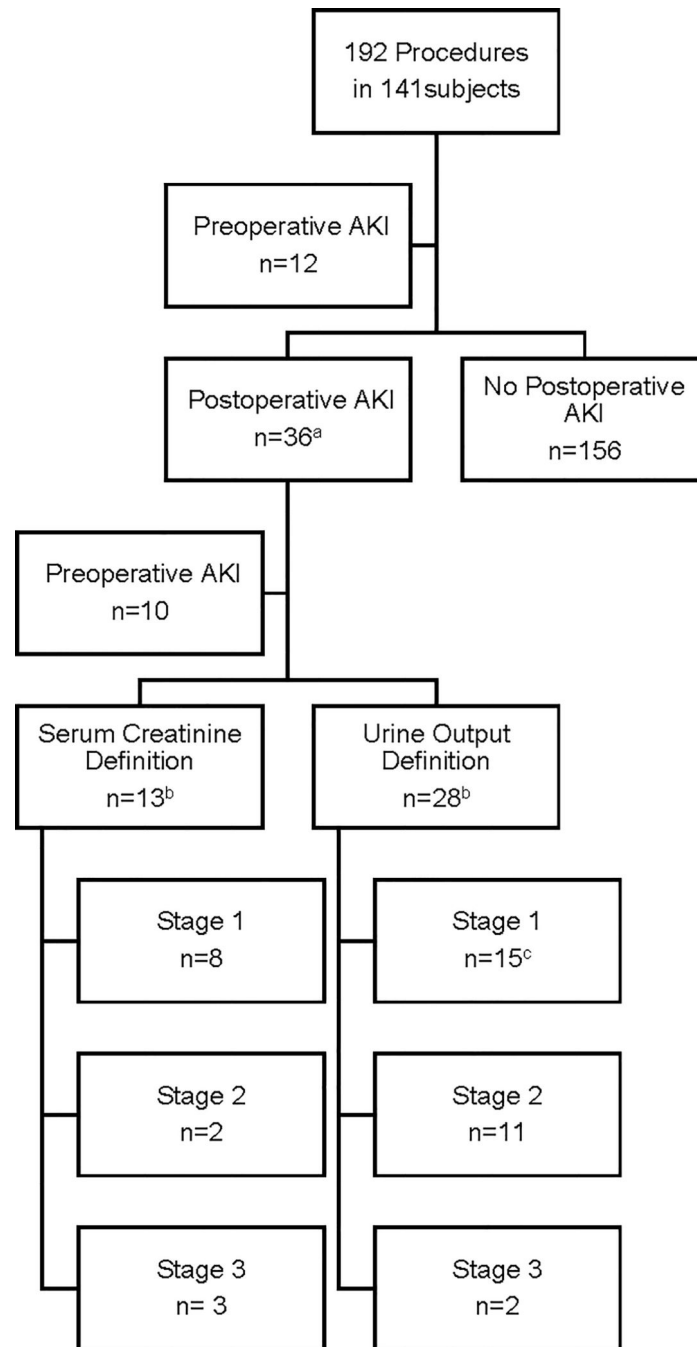


Figure 2, online

Study Flow Diagram of AKI in Enrolled Subjects

Abbreviation: Acute Kidney Injury, AKI.

^a Three subjects had recurrent AKI at a subsequent procedure during their hospitalization

^b Five subjects met criteria for both definitions.

^c One subject did not meet criteria by 2014 neonatal Kidney Diseases Improving Global Outcomes, but did meet criteria of 2017 neonatal Kidney Diseases Improving Global

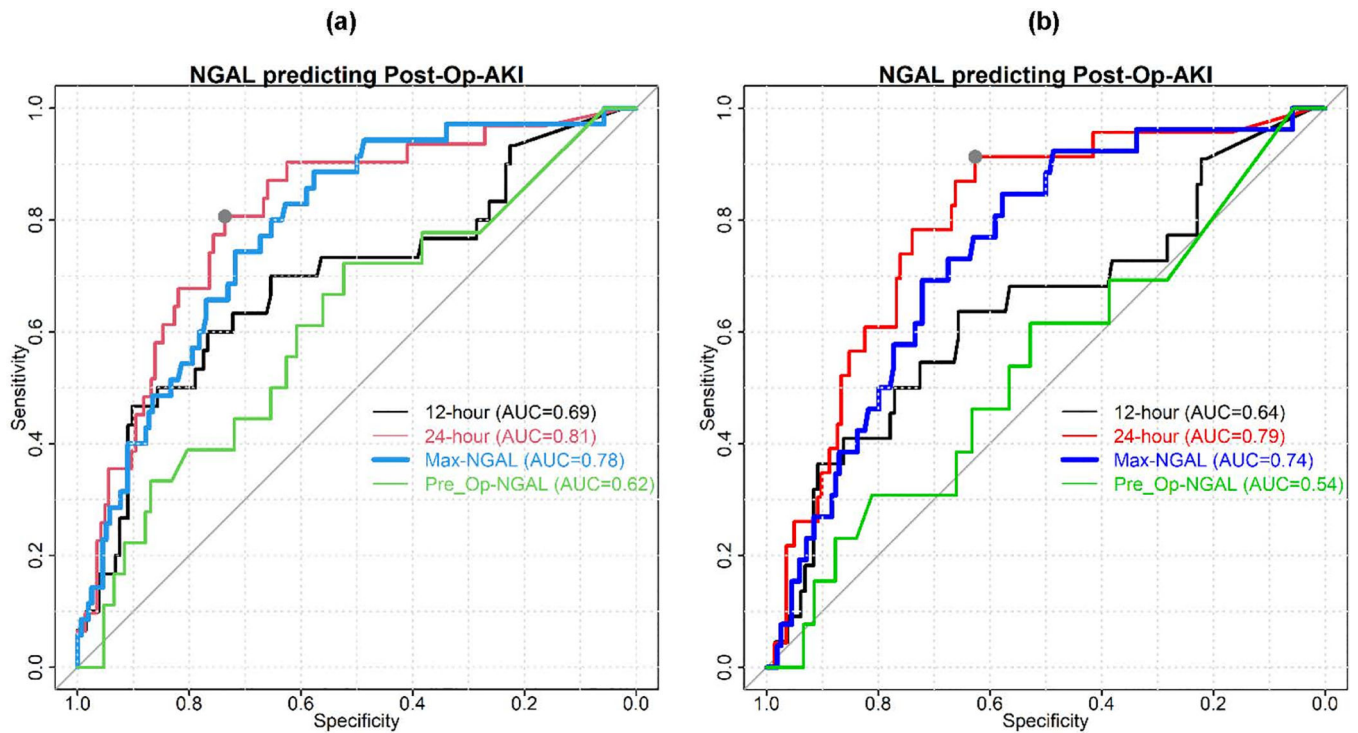
Outcomes with urine output < 1 mL/kg/hour consistently over 24 hours, but >0.5 and was subsequently included

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	Time	Cut-off concentration ^a	Specificity	Sensitivity	AUC
(a) Following all procedures	Pre-Op	29	0.52	0.72	0.62
	12 hours	498	0.90	0.47	0.69
	24 hours	144	0.74	0.81	0.81
	Peak	162	0.58	0.89	0.78
(b) Excluding procedures with pre-operative AKI	Pre-Op	29	0.53	0.62	0.54
	12 hours	44	0.66	0.64	0.64
	24 hours	81	0.63	0.91	0.79
	Peak	162	0.58	0.85	0.74

Figure 3.

ROC curves for predicting postoperative AKI status using urinary NGAL concentrations at different time.

^ang/mL

(a) Represents AUC-ROC curves for uNGAL concentrations from cohort regardless of preoperative AKI, (b) Represents AUC-ROC curves for uNGAL concentrations with exclusion of subjects with preoperative AKI

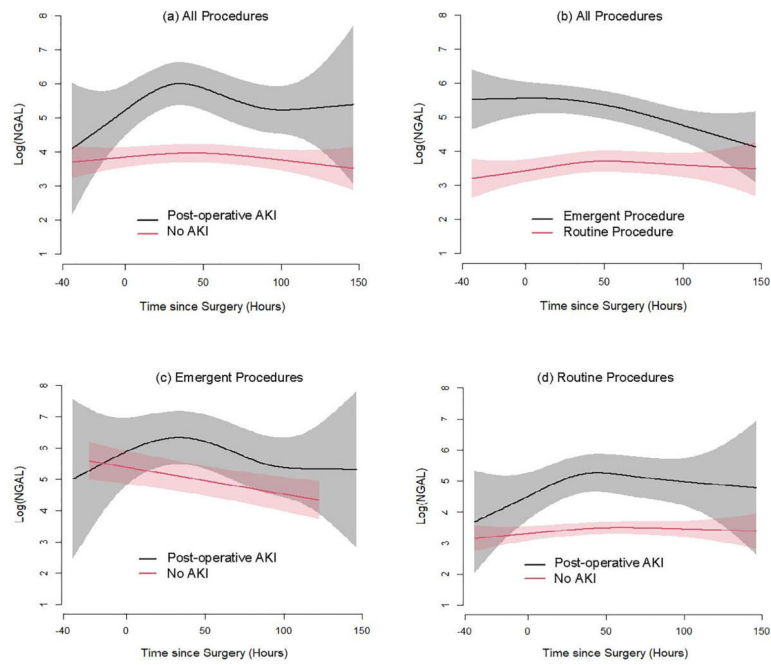


Figure 4.

Log transformed trajectory of uNGAL concentrations

Abbreviations: Acute Kidney Injury, AKI

Log transformed trajectory of uNGAL concentrations and associated 95% confidence intervals in (a) *all procedures separated by postoperative AKI and no AKI* (b) *all procedures separated by emergent procedure and routine procedure* (c) *emergent procedures separated by postoperative AKI and no AKI* (d) *Routine procedures separated by postoperative AKI and no AKI*

Table 1.2014 Neonatal Modified KDIGO Criteria^{1,2}

Stage of AKI	Serum Creatinine Definition	Urine Output Definition ^a
1	0.3 mg/dL rise within 48 h <i>or</i> rise of 1.5–1.9 × reference SCr within 7 days	<0.5 mL/kg/hr for 6–12 hr
2	rise of 2 to 2.9 × reference SCr	<0.5 mL/kg/hr for 12 hr
3	rise of 3 × reference SCr <i>or</i> 2.5 mg/dL or dialysis	<0.3 mL/kg/hr for 24 hr <i>or</i> anuria for 12 hr

Abbreviations: SCr, serum creatinine; Reference SCr is the lowest prior serum creatinine

^aOne subject did not meet urine output criteria as documented above but met the 2017 retrospective Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) neonatal modified Kidney Diseases: Improving Global Outcomes definition over 24 hours with urine output consistently 0.6 mL/kg/hour and was subsequently included.

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Table 2.

Perioperative Procedural Characteristics between Acute Kidney Injury (AKI) and No AKI

	No AKI (n=156)	AKI (n=36)	^a <i>p</i> value
Preoperative			
^b GA at birth in weeks, median [IQR]	35 [31, 37]	35 [29, 37]	0.079
CGA in weeks, median [IQR]	40 [36, 45]	38 [35, 41]	0.026
^b Male Sex, n (%)	83 (53%)	15 (42%)	0.216
^b Race, n (%)			0.354
White	129 (83%)	26 (72%)	
Black	20 (13%)	7 (19%)	
Other	7 (5%)	3 (8%)	
^{bc} Known Renal Anomaly, n (%)	28 (18%)	8 (22%)	0.555
Past Medical History of AKI, n (%)			
Yes	31 (20%)	15 (41.72%)	0.025
No	97 (62%)	15 (41.7%)	
Unknown	28 (18%)	6 (16.6%)	
Preoperative Diagnosis, n (%)			
Bowel Obstruction or Atresia	17 (11%)	5 (14%)	0.244
Acute NEC or Intestinal Perforation	14 (9%)	9(25%)	
Esophageal Atresia/ Tracheoesophageal fistula	18 (12%)	5 (14%)	
Omphalocele	5 (3%)	1 (3%)	
CDH	14 (9%)	3 (8%)	
Gastroschisis	20 (13%)	2 (6%)	
Short Bowel Syndrome/ Intestinal Failure	10 (6%)	3 (8%)	
^d Other	58 (37%)	8 (22%)	
Preoperative Nephrotoxic Medication Exposure, Yes (%)	27 (19%)	12 (37%)	0.032
Intervention			
Emergent Procedure, Yes (%)	47 (30%)	23 (64%)	<0.001
Surgical approach, n (%)			
Laparotomy	83 (53%)	27 (75%)	0.520
Thoracotomy	16 (10 %)	3 (8.3%)	
Laparoscopy	21 (14%)	0	
Thoracoscopy	9 (6%)	3 (8.3%)	
Other	27 (17%)	3 (8.3%)	
Duration of Anesthesia in minutes, median [IQR]	213 [168,295]	220 [151, 317]	0.814
Intra-operative Nephrotoxic Medication Exposure, Yes (%)	31 (20%)	6 (17%)	0.661
Postoperative			
# of Postoperative SCr obtained, median [IQR]	3 [2,4]	5 [4,8]	<0.0001
^d Postoperative Nephrotoxic Medication Exposure, Yes (%)	42 (27%)	15 (42%)	0.086

	No AKI (n=156)	AKI (n=36)	^a <i>p</i> value
^e Days of Nephrotoxic Medication Exposure to postoperative day 5, median [IQR]	2 [1,3]	3 [2,4]	0.030

Abbreviations: GA, Gestational Age; CGA, Corrected Gestational Age; IQR, interquartile range; NEC, Necrotizing Enterocolitis; CDH, Congenital Diaphragmatic Hernia; SCr, Serum Creatinine

^a Analysis performed using a univariate mixed effect models where subjects were used as a random effect to account for multiple procedures per patient

^b Characteristics are described per procedure and individual subjects may have had more than one procedure

^c Renal Anomalies include: Vesicoureteral reflux, Ectopic kidney, Renal cortical cysts, Pelviocaliectasis, Hydronephrosis, Dilated ureter with hydronephrosis, Hyperechogenic kidney, Horseshoe kidney, Unilateral multicystic dysplastic kidney, Cross fused ectopia, Ureterocele, Solitary kidney

^d Diagnoses include: Anorectal malformation, Bronchial atresia, Bronchogenic cyst, Cloacal malformation, Choledochal cyst, Congenital pulmonary airway malformation, Foreign body, Hernia, Mass/tumor, Pyloric stenosis

^e Acyclovir, Amphotericin, Aspirin, Captopril, Cidofovir (up to 7 days prior), Enalapril, Gentamicin, Indomethacin, Contrast (up to 7 days prior), Nafcillin, Piperacillin/tazobactam, Tobramycin, Valacyclovir, Valganciclovir, Vancomycin⁴¹

Table 3.

Median (IQR) uNGAL concentrations (ng/mL) collected at pre- and postoperative time points in No AKI vs. AKI

	Preoperative (n=119)	12-hour (n=153)	24-hour (n=165)	36-hour (n=163)	48-hour (n=161)	72-hour (n=163)	96-hour (n=146)
<i>All Procedures</i>							
No AKI (n=156)	26.4 (9.4, 101.0)	27.2 (11.2, 120.0)	37.7 (12.0, 159.5)	38.8 (14.4, 131.0)	41.5 (13.9, 123.0)	32.6 (12.7, 92.4)	31.5 (10.2, 89.1)
AKI (n=36)	59.4 (14.3, 174.0)	244.0 (18.5, 1410.0)	292.0 (164.0, 2440.0)	243.0 (82.4, 1890.0)	290.0 (41.9, 2030.0)	131.5 (40.7, 419.0)	131.0 (44.3, 442.0)
<i>p</i> value	0.1181	0.0009	<0.0001	<0.0001	0.0004	0.0004	<0.0001
<i>Excluding procedures of interest in subjects with pre-operative AKI</i>							
No AKI (n=154)	26.4 (9.4, 94.0)	27.2 (11.2, 120.0)	33.8 (12.0, 156.0)	38.8 (15.4, 131.0)	42.7 (14.0, 124.0)	32.6 (12.6, 88.3)	30.9 (10.2, 87.3)
AKI (n=26)	35.5 (9.4, 120.0)	136.6 (12.3, 699.0)	284.0 (148.0, 1350.0)	205.0 (56.6, 799.0)	98.1 (31.6, 1520.0)	105.0 (47.5, 272.0)	105.2 (45.5, 359.0)
<i>p</i> value	0.650	0.0356	<0.0001	0.0001	0.0429	0.0018	0.0017

Abbreviations: Acute Kidney Injury, AKI