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Clinical impact of severe acute kidney injury on post-operative and brain injury outcomes in preterm infants following surgical necrotizing enterocolitis

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Abstract

Background: To evaluate post-operative outcomes and white matter injury (WMI) using brain MRI at term equivalent in neonates with and without severe acute kidney injury (AKI) following surgical necrotizing enterocolitis (NEC).

Methods: A retrospective cohort study comparing neonates with severe (Stage 2/3) vs. other (no AKI/Stage 1) AKI using KDIGO classification with multivariable models assessing this association in the context of multiple systemic comorbidities.

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Disclosure statement

The authors disclose no conflicts. All authors declare no real or perceived conflicts of interest that could affect the study design, collection, analysis, and interpretation of data, writing of the report, or the decision to submit for publication. PMG designed the study; PMG, AB, JP, DA collected and analyzed the data; MZ and WBH participated in the data analysis. PMG, DA, MZ, WBH, JFP, and KS wrote the article. All the authors approved the manuscript. For full disclosure, we provide here an additional list of other author's commitments and funding sources that are not directly related to this study: David J Askenazi is a consultant for Baxter, Nuwellis, Medtronic Bioporto, the AKI Foundation, and SeaStar. In addition, he receives grant funding for education and studies not related to this project from Baxter, Nuwellis, and Medtronic. He has patents pending in the area of urine collection and kidney support therapy.

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Informed consent

Patient consent was not required as per IRB.

Results: Of 103 neonates with surgical NEC, 60 (58%) had severe AKI. Those with severe AKI had lower birth weight (BW; 715 vs. 950g; $p = .023$), more frequently treated with indomethacin (18.3 vs. 2.4%); $p = .014$), higher CRP levels at 24 h after NEC onset (14.4 [6.4–19.8] vs. 4.8 [1.6–13.4]; $p = .005$), higher presence of cholestasis (73.3 vs. 51.2%); $p = .023$), later age of NEC onset (14 vs. 7d); $p = .004$), longer length of bowel resected (14.9 vs. 4.3 cm); $p = .011$), longer post-operative ileus days (14 vs. 9d); $p < .001$), longer post-operative days at starting enteral feedings (15 vs. 10 d; $p < .001$), longer days of attainment of full enteral feedings (75 vs. 44.5 d; $p = .008$) and longer length of stay (140.5 vs. 94 d; $p = .028$) compared to those without severe AKI. Compared to infants without AKI by serum creatinine, those with AKI had significantly more cases of white matter abnormality (WMA; 90 vs. 36.6%; $p < .001$) and retinopathy of prematurity (63.9 vs. 35.3%; $p = .017$). In addition, the presence of AKI Stage 2 and 3 by serum creatinine was independently associated with higher odds of sustaining severe WMI level on an ordinal scale (OR = 6.2; 95% CI = (1.1–35.5); $p = .041$).

Conclusions: Neonates with severe AKI following surgical NEC were more likely to experience longer post-operative morbidity and higher WMI by MRI at term.

Keywords

Acute kidney injury; brain injury; postoperative outcomes; preterm infants

Introduction

Necrotizing enterocolitis (NEC) affects 6–10% of preterm infants with a birth weight (BW) less than 1500 g [1,2]. NEC remains a leading cause of death among preterm neonates and leads to increased hospital care and economic burden [3-9]. NEC is one of the most common conditions requiring emergency surgery in a neonatal intensive unit. NEC is associated with a septic shock-like clinical picture and severe systemic inflammatory response that can contribute to multi-organ dysfunction due to intravascular volume depletion, capillary leak syndrome, and hypotension [10]. These hemodynamic changes, surgical stresses, anesthetic agents, and nephrotoxic medications are associated with acute kidney injury (AKI), especially in premature neonates [11]. The impact of NEC on underdeveloped premature kidneys has not been addressed. Animal models of AKI (the cecal ligation and puncture model) and an NEC mouse study have demonstrated that NEC is associated with widespread kidney inflammation [12,13].

AKI affects approximately 30% of neonates admitted to the NICU. They require intravenous fluids and are associated with poor clinical outcomes such as prolonged stay and increased mortality in premature and term neonates [14,15]. Preterm infants with surgical NEC have been shown to have greater pro-inflammatory markers in the serum, severe brain injury, and poor neurodevelopmental outcomes at two years follow-up [16-20]. Many cohort and randomized trials report AKI predicts clinical outcomes in neonatal and pediatric populations with congenital cardiac disease undergoing surgery and cardiopulmonary bypass [21-23]. Following surgical NEC diagnosis, the risk factors for AKI, such as sepsis, hypotension, and nephrotoxic agents, have been previously reported [13,24-30]. Our previous retrospective observational cohort study reported the demographics and clinical

outcomes associated with severe AKI in preterm infants with NEC [31] at our institution between 2013 and 2018.

In this report, we have examined the association of severe AKI with other important markers of neonatal morbidity in surgical NEC patients. Compared to prior reports from our group and others, we have carried out a more comprehensive evaluation of a post-operative clinical course and severity of brain abnormality differences between premature surgical NEC neonates with and without severe AKI. This evaluation includes detailed multivariable models assessing whether the presence of AKI in surgical NEC neonates was independently associated with worse post-operative and brain outcomes. Our primary hypotheses were that severe AKI would be independently associated with the prolonged post-operative recovery and severe white matter abnormalities on term equivalent brain MRI, accounting for other known and unknown predictors of adverse outcomes in neonates suffering from surgical NEC.

Methods

Population and study design

The study was conducted at the University of Mississippi Medical Center (UMMC) Neonatal Intensive Care Unit, a Level IV unit with approximately 900–100 admissions yearly and referrals from the entire state. The UMMC Institutional Review Board has approved this retrospective cohort study, with a waiver of informed parental consent to collect clinical data. All infants admitted between January 2013 and 31 December 2018, with an NEC diagnosis (Bell Stage 3) were included in the study [32]. Neonates diagnosed with medical NEC, kidney anomalies, congenital heart disease, spontaneous intestinal perforation, and intestinal atresia were excluded from the analysis.

Demographic and clinical information

We collected demographic data, including BW, gestational age (GA), appropriate for gestational age status (AGA), race, and sex, mode of delivery, outborn status, and Apgar score 6 at 5 min. We also gathered maternal information, including chorioamnionitis, antenatal steroids, and pregnancy-induced hypertension (PIH). Additional clinical data included patent ductus arteriosus (PDA), frequency of PDA surgical ligation, duration of mechanical ventilation, inotrope (dopamine) use 24 h after NEC onset, and ibuprofen/indomethacin treatment (before NEC). Our unit does not use Indocin for IVH prophylaxis. Sepsis-related variables included blood culture-proven sepsis at NEC onset and duration/type of antibiotics. We also collected information on the frequency of cholestasis (direct bilirubin >2 mg/dL) at any time after NEC diagnosis.

NEC information

NEC was defined using Bell's criteria [32], and diagnosis of NEC was made on abdominal X-ray findings, including portal venous gas, pneumatosis, and pneumoperitoneum. The frequency of Bell stage III/surgical NEC was gathered [32]. In addition, we recorded information on the age of NEC diagnosis and the fulminant NEC [33]. Our surgical care and team for managing the NEC remained without much significant change throughout the study

duration. We also recorded information on short bowel syndrome (parenteral nutrition >90 d) and surgical morbidity. The surgical morbidity was classified as strictures, fistulas, wound dehiscence, surgical site infections (including abscesses), adhesions, and perforations.

Kidney function data

The Modified Neonatal Staging Criteria described in the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI was used to determine the incidence of kidney injury [11,14,34-36]. We examined all SCr measurements and daily UOP the day before NEC diagnosis, at NEC onset, 24, 48, 72, 96 h, and 7 d following NEC diagnosis. Baseline SCr was defined by the lowest SCr documented in the patient's clinical record before NEC onset.

Stage 1, AKI was defined as a rise in SCr by 0.3 mg/dL or 1.5–1.9 times above baseline and/or UOP <1 mL/kg/h over the last 24 h. Stage 2, AKI was defined as an increase in SCr 2–2.9 times above baseline and/or UOP <0.5 mL/kg/h. Stage 3, AKI was defined as an increase in SCr 3 times above baseline or SCr >2.5 mg/dL and/or and UOP <0.3 mL/kg/h [36]. The maximum stage AKI was defined by the highest SCr or UOP AKI stage within 4 d after NEC onset. At our center, laboratories measure SCr using the isotope dilution mass spectrometry method. The weighed diapers recorded by bedside nurses in the patient chart were used to collect UOP data. We stratified infants as with severe (Stage 2 and 3 AKI) and without severe (no AKI or Stage 1 AKI) as has been done in previous clinical studies [14,37].

Outcome data

Post-operative information, such as post-operative ileus days (defined as infants being NPO after bowel surgery), time to reach full feeds (>120 mL/kg/d), total parenteral nutrition days, length of stay, and hospital mortality were measured. We defined mortality as death due to any reason prior to hospital discharge.

Neonatal MRI data

Brain MRI without contrasts was routinely obtained at corrected age of 36 weeks, or before discharge, whenever clinically indicated, in all infants with BW less than 1500 g per routine hospital clinical practice. The most common reason for not obtaining MRI was death or transfer to a higher center for bowel transplantation. All term equivalent age (TEA) MRI scans were scored independently by two pediatric neuro-radiologists aware of the infants' clinical diagnosis, however unaware of the initial reported clinical read of Brain MRI findings. We used a scoring system consisting of eight scales for white and gray matter injury developed by Woodward et al. [17]. An objective visual scoring system was used instead of automated software, such as FreeSurfer, which requires acquisition of 3D isovoxel volumetric MRI sequences of the brain. The majority of the brain MRIs performed in this group of patients were 2D non-isovoxel sequences tailored to a faster brain MRI protocol that is used in non-sedated infants. An analysis of any disparities between the initial clinical read and radiologist scoring of white matter loss, gray matter injury, and cerebellar injury was not performed.

We recorded data on cranial ultrasound (CUS) findings from the patient's clinical record before and after NEC onset. The information was collected on the presence and extent of white-matter echolucency or cystic periventricular leukomalacia, ventriculomegaly, and the highest grade of intraventricular hemorrhage before and after the NEC onset.

Neurodevelopment assessment at two years of age

All infants are routinely offered a comprehensive neurodevelopmental evaluation. Specialists use the Bayley Scales of Infant Development (BSID-III) for all neurodevelopmental assessments. In addition, we recorded psychomotor and cognitive development assessment scores from the clinical record [17].

Statistical methods

We summarized the data as mean and standard deviation (\pm SD) for parametric continuous variables. Comparisons between infants with severe AKI and without severe AKI were performed using Student's t-test, Welch's t-test, and/or ANOVA depending on equality of the variances. For data not normally distributed, median with interquartile range (IQR) [1st quartile; 3rd quartile] estimates were calculated with group differences tested using Kruskal–Wallis test or Mann–Whitney U test. Categorical data were summarized as counts with frequencies as percentages, and group differences were tested using the Chi-squared test or Fisher's exact test [38]. Association between serum creatinine and urine output criteria for AKI was assessed with the Jonckheere–Terpstra test of ordinal trend and the weighted kappa measure for agreement [39]. Cumulative and multivariable logistic regression was performed to evaluate whether AKI by serum creatinine was an independent risk factor for WMA. For cumulative logistic regression, probabilities modeled are cumulated over the lower ordered values. The odds ratio for continuous variables are expressed per standard deviation of that factor. A p value $< .05$ was considered significant. The statistical tests were performed in SAS version 9.4 (SAS Institute, Cary, NC).

Results

Cohort characteristics

Of the 227 infants evaluated with possible NEC diagnosis, 103 met the inclusion criteria of surgical NEC, while 124 were excluded due to medical NEC or did not meet other inclusion criteria (see Figure 1). The cohort of 103 neonates with surgical NEC had a median (IQR) GA of 26.4 (24.3 – 29.6) weeks, median BW of 780 (650 – 1180) g, was predominantly male (68/103, 66%), African American (77/103, 74.8%), and outborn (63/103, 61.2%). The remaining demographic information is summarized in Table 1.

NEC data

The median (IQR) NEC onset age was 10 (5 – 23) d. Eighteen neonates (17.5%) had fulminant NEC. The abdominal x-ray showed pneumatosis in 48/103 (46.6%), pneumoperitoneum 55/103 (53.4%), and portal venous gas in 8/103 (7.8%) cases. Forty-one cases were treated with a Penrose drain, and 71/103 (68.9%) required laparotomy in less than 48 h after the NEC onset. The median length of bowel resected was 12 (3.2 – 28.8) cm. Of these, 43/86 (50%) later developed short bowel syndrome. At NEC onset, 88/103 (88%)

required assisted ventilation, and 80/103 (77.7%) required inotropic support with dopamine within 24 h of presentation. Among the cases of surgical NEC, 59/103 (57.3%) neonates had PDA, in whom 12/102 (11.8%) had received treatment with cyclooxygenase (COX) inhibitors (indomethacin/ibuprofen) before NEC onset. Blood culture-positive sepsis at the time of NEC onset was seen in 32/103 (31.1%) cases and required antibiotics for a mean time of 9.0 ± 4.8 d. Additional post-operative and clinical characteristics among the patients of NEC are summarized in Tables 1, 3, and 4.

Acute kidney injury

Of the 103 neonates with surgical NEC, 77/103 (74.8%) had AKI by KIDGO criteria. Twenty-six (25.2%) had no AKI, 23/103 (22.3%) had stage 1, 31/103 (30.1%) had Stage 2, and 17/103 (16.5%) had AKI Stage 3 by either highest UOP or SCr staging criteria. The severe AKI (Stage 2 and 3) occurred in 60/103 (58.3%) while 43/103 (41.7%) had Stage 0 and 1 AKI (non-severe). Among those with severe AKI, 15 had AKI by SCr alone, 29 had AKI by UOP only, and 16 had AKI by SCr and UOP (Table 2).

Table 1 also compares baseline demographic characteristics and clinical factors between participants defined with vs. without severe AKI by UOP and/or SCr criteria. Comparing those without severe AKI, infants with severe AKI had significantly lower median (IQR) BW (715 g [625–990] vs. 950 g [690–1600]; $p = .023$), received Indomethacin more frequently (18 vs. 2.38%; $p = .014$), more cholestasis (direct bilirubin >2 mg/dL) at NEC onset (73.33 vs. 51.22%; $p = .023$), higher level of CRP at 24 h after NEC onset (14.4 [6.4–19.8] vs. 4.8 [1.6–13.4]; $p = .005$) and higher level of CRP at 48 h after NEC onset (15.7 [6.65–24.5] vs. 4.4 [2.4–19.8]; $p = .012$).

Those with severe AKI had older age onset (14 [8–23] vs. 7d [4–13]; $p = .004$), lower presence of pneumoperitoneum (45 vs. 65%; $p = .044$) and longer length resected bowel (14.9 cm [8–32] vs. 4.25 cm [2–27.2]; $p = .011$). Small bowel resection was significantly more frequent (66.7 vs. 58.8%; $p = .04$) in those with severe AKI. The other NEC features are summarized in Table 3.

Post-operative outcomes

Neonates with severe AKI had a significantly longer period of post-operative ileus (14 d [12–20] vs. 9d [7–14]; $p < .001$), took a long time to reach full feeds (75 d [43–109] vs. 44.5 d [26–68.5]; $p = .008$) and had a longer post-operative day at starting enteral feedings (15 d [13–23] vs. 10 d [8–15]; $p < .001$) than to those without severe AKI. Any mechanical ventilation (94.8 vs. 78.6%; $p = .027$) and pressor support at 24 h (88.3 vs. 62.8%; $p = .002$), and length of hospitalization (141 d [88–180] vs. 94 d [55–161]; $p = .028$) were all significantly higher neonates with severe AKI compared to those without severe AKI. The additional post-operative outcomes are summarized in Table 4.

Brain injury and AKI

In our cohort, 61 infants had brain MRI results available for analysis. Of the 61 infants, 33/61 (54.1%) had some white matter abnormality (WMA) (15/61 (24.6%) had mild WMA, 12/61 (19.7%) had moderate WMA, and 6/61 (9.8%) had severe WMA on term equivalent

brain MRI). The infants with severe AKI had significantly more cases of WMA (90 vs. 36.6%; $p < .001$) and retinopathy of prematurity (63.9 vs. 35.3%; $p = .017$) than those without severe AKI by serum creatinine. The findings are summarized in Table 5.

The neonates with severe AKI by serum creatinine had significantly more grade 2 loss of periventricular volume (65 vs. 30%; $p < .001$), grade 2 ventricular dilatation (65 vs. 25%; $p = .001$), grade 2 thinning of Corpus Callosum (65 vs. 27.5%; $p = .004$) compared to neonates without AKI. In addition, seven infants (7/60, 11.7%) had grey matter abnormalities. These infants mainly showed loss of subarachnoid space grade 1 (47/60, 78.3%), grey matter signal abnormality grade 1 (51/60, 85%), and grade one gyral maturation changes (52/60, 86.7%). The data has been summarized in Table 6.

Two-year neurodevelopment follow-up

Out of 103 patients, 18 infants had neurodevelopment follow-up in a high-risk clinic at two years of age. Among those 18 patients, no significant findings in neurodevelopment outcomes between AKI presence and AKI absent patients were found. The results are summarized in Supplemental Table 1.

AKI independent effect assessment

While holding all other variables constant, the presence of AKI Stage 2 and 3 by serum creatinine was independently associated with higher odds of sustaining a more severe ordinal grade of white matter injury (WMI; OR = 6.2; 95% CI = (1.1–35.5); $p = .041$). In contrast to the grade of WMI, AKI Stage 2 and 3 by serum creatinine was numerically but not independently significantly associated with the binary presence of any WMA (OR = 12.9; 95% CI = (0.7–241); $p = .09$) in this multivariable analysis. Similarly, AKI Stage 2 and 3 by serum creatinine was numerically but not independently significantly associated with the presence of binary grade 3 or 4 WMA vs. Grade 1 or 2 WMA (OR = 9.8; 95% CI = (0.8–116); $p = .072$). Detailed results are summarized in Table 7 and Appendix Q. For the subset of 28 with US data, AKI Stage 3 or 4 by serum creatinine remained a significant predictor for higher grades of WMBI (OR = 14.9 [95% CI: 2.3, 98.7], $p = .005$ adjusted for ordinal severity of IVH on head US).

Discussion

Our study evaluated the association between AKI in patients with surgical NEC and the early post-operative outcomes, WMI outcomes, and neurodevelopmental outcomes at two years of age. We have previously shown that neonates with surgical NEC who had severe AKI had a significantly longer length of hospitalization. Those with severe AKI were outborn, received more antenatal steroids, and had blood culture-positive sepsis at NEC onset [31]. This report provides a broader understanding of the outcomes in those with severe AKI. Although this study did not show a statistically significant difference in the mortality rates between those with severe AKI vs. non-severe/no AKI (31.6 vs. 30.2%; $p = .877$), we document significant morbidity in the neonates with severe AKI. Most notably, within this cohort, severe AKI was significantly associated with treatment with indomethacin, higher CRP levels at 24 h after NEC onset, higher presence of cholestasis,

higher age of NEC onset, a longer length of bowel resected, longer post-operative ileus days, more days before attainment of full enteral feedings, and longer of hospitalizations.

Our data also shows that severe AKI is significantly and independently associated with a more severe level of WMA (OR = 6.2; 95% CI = (1.1–35.5); $p = .041$). Consistent with this finding in direction and magnitude, severe AKI was numerically associated with any WMA (OR = 12.9; 95% CI = (0.7–241); $p = .09$) and severe Grade 3 or 4 WMA (OR = 9.8; 95% CI = (0.8–116); $p = .072$). While the numerical results from all three multivariable analyses are similar in direction and magnitude, the “loss of information” from collapsing ordinal information into binary categories and inherently limited single-center sample size/power (as evident from the wide odds ratio confidence intervals) for a relatively rare condition likely accounts for the lack of statistical significance in the binary *vs.* ordinal analyses.

Severe AKI (Stage 2 and 3) was observed in 58% of our cohort, which was higher than the incidence of KIDGO-defined AKI Stage 2 and 3 from the Assessment of Worldwide AKI Epidemiology in *Neonates* study (16%), one of the largest neonatal AKI study [14]. Previously published studies of neonates with NEC have estimated any AKI incidence of 39–54% primarily by serum creatinine criteria [28–30]. By KIDGO criteria, 75% had any AKI. While AKI by SCr criteria is similar in our surgical NEC cohort to these prior reported medical and surgical NEC cohorts, the addition of the KIDGO urine output criteria may increase the sensitivity to detect AKI.

In our cohort, infants with severe AKI had significant post-operative morbidities. These infants took four weeks longer to reach full enteral feeding and wean from parenteral nutrition. In addition, the infants with severe AKI had median post-operative ileus five days longer than other groups, which may be explained due to bowel wall edema due to decreased kidney function in the severe AKI group. However, we do not know much AKI is associated with long-term morbidities, such as time to reach full feeds or duration of parenteral nutrition. These long-term morbidities may be more related to intestinal factors, such as length of bowel loss after laparotomy. Unfortunately, there is no study reporting these morbidities in preterm infants undergoing abdominal surgery.

Several reports show that severe AKI is associated with prolonged hospitalization in other sick pediatric populations, even when adjusting for the disease severity [40,41]. In this cohort, we noted that severe AKI had 46 days longer NICU hospital stay (141 d [88–180] *vs.* 94 d [55–161]; $p = .028$).

In our study, infants with severe AKI by serum creatinine had higher rates of white matter abnormalities on term equivalent brain MRI (90 *vs.* 36.6%; $p < .001$). In the small sub-cohort available for longer-term assessment, significantly lower Bayley neurodevelopmental scores were observed at two years of corrected age. We noticed that periventricular volume loss and Grade 2-periventricular dilation were predominant lesions on brain MRI. In our cohort, AKI is significantly and independently associated with a more severe ordinal level of WMA [42]. These findings suggest AKI may be more than just a confounder or epiphenomenon merely associated with other clinical and demographic causal factors determining outcome in preterm infants with surgical NEC. Although there are several

possible explanations for our findings, some of the possible reasons for our observed associations between AKI and brain injury result from both hypovolemic insults as well as systemic inflammation. Hypovolemia would result in AKI and ischemic brain injury from compromised perfusion. The AKI is likely not to be an isolated phenomenon but instead represents remote multi-organ dysfunction involving the lungs, heart, liver, brain, and intestine through inflammatory pathways involving increased oxidative stress, neutrophil migration, and cytokine expression shown in animal studies [43]. Several studies have shown that preterm infants with surgical NEC have severe WMI on the brain MRI, higher serum pro-inflammatory markers, and poor neurodevelopmental outcome at two years of corrected age [16-20]. Animal studies have reported surgical NEC leads to systemic inflammation and causes neuronal injury *via* microglial activation, inflammatory pathway activation, and brain barrier disruption [44-47]. Mechanistically, we hypothesize that severe AKI in neonates with surgical NEC may exacerbate the brain injury by acting as a catalyst or modifier of neuro-inflammation. Further studies are needed to understand the role of severe kidney injury with brain injury in neonates with NEC.

We observed severe brain injury in neonates with AKI by serum creatinine compared to AKI by urine output. Rapid recovery of urine output within 24 h after NEC onset may explain this observation, which needs further study. In contrast, higher serum creatinine indicates severe kidney injury, which takes longer to recover [31]. In our cohort, as in other published studies [36,48,49], there was no significant association or agreement between serum creatinine and urine output criteria for diagnosing AKI. The criteria for diagnosing AKI in neonates deserve further investigation in large multi-center studies.

The strengths of this study include a detailed description of the largest reported (to our knowledge) consecutive cohort of neonates with surgical NEC. This description includes contemporary measures of neonatal AKI, brain MRI findings, detailed post-operative course measures, laboratories, and 2-year Bayley neurodevelopmental outcomes in a small but important sub-cohort. We successfully captured the urine output data, which was not included in previously published reports. Additionally, severe AKI determined by serum creatinine was a more helpful predictor than AKI by urine output. Our data may help guide bedside management and risk stratification of patients with surgical NEC and counseling families for short-term and long-term outcomes.

Limitations include a single-center experience, perhaps reducing the study's generalizability. In this Mississippi-based cohort, 75% of the neonates with surgical NEC were African American. While this is likely partly due to the demographics of Mississippi, this may also be related to adverse social determinants of health and/or genetic risk for kidney disease. We did not have complete data of pre-NEC head ultrasound. However, in the subset of surgical NEC neonates with complete US data, US status does not appear to be a significant confounder explaining the observed AKI and WMI severity significant association. The diaper weights to reflect UOP also leads to measurement limitations. This may have affected the agreement between serum creatinine and urine output AKI definitions. We did not have anesthesia exposure data to evaluate its effect on the brain outcomes [50]. The retrospective study design lacks uniformity and completeness in each neonate's available data, including incomplete follow-up after discharge. Finally, NEC is a relatively rare condition. While ours

is a relatively high volume neonatal intensive care unit center, sample size also limits our power to detect associations between clinical factors, NEC, AKI, and outcomes. Further, multiple comparisons yield a higher probability of type I errors. While our multivariable analyses suggest otherwise, the significant and numerical associations observed between severe AKI had brain injury on the brain MRI may still plausibly arise from confounding with other known, unmeasured, and/or unknown factors.

Conclusion

In conclusion, neonates with severe AKI had significant post-operative morbidities and white matter abnormalities on the brain MRI compared to those without severe AKI. While severe AKI may plausibly be just a marker of severe illness remains, data and multivariable analyses from our surgical NEC experience credence to the alternative hypothesis that severe AKI contributes causally to greater morbidity and prolonged postoperative clinical course and slower recovery in neonates with surgical NEC.

Future direction

In the future, both retrospective and prospective studies (particularly multi-center to enhance sample size) with additional clinical data (e.g. end-organ (kidney and brain) perfusion by near-infrared spectroscopy [51]) and functional/tubular urinary and brain biomarkers, which may help providers predict AKI and brain injury at an early stage. Studies that evaluate kidney protective strategies to prevent AKI and neuroprotective strategies to prevent brain injury and its consequences are needed to improve the post-operative recovery clinical and neurodevelopmental outcomes in neonates with surgical NEC. There is a need to develop a scoring system including AKI to identify the high-risk neonates with advanced NEC and develop improved therapeutic options. These high-risk infants with severe AKI should be followed post-discharge with a pediatric nephrologist and developmental specialist to identify long-term sequelae, including chronic kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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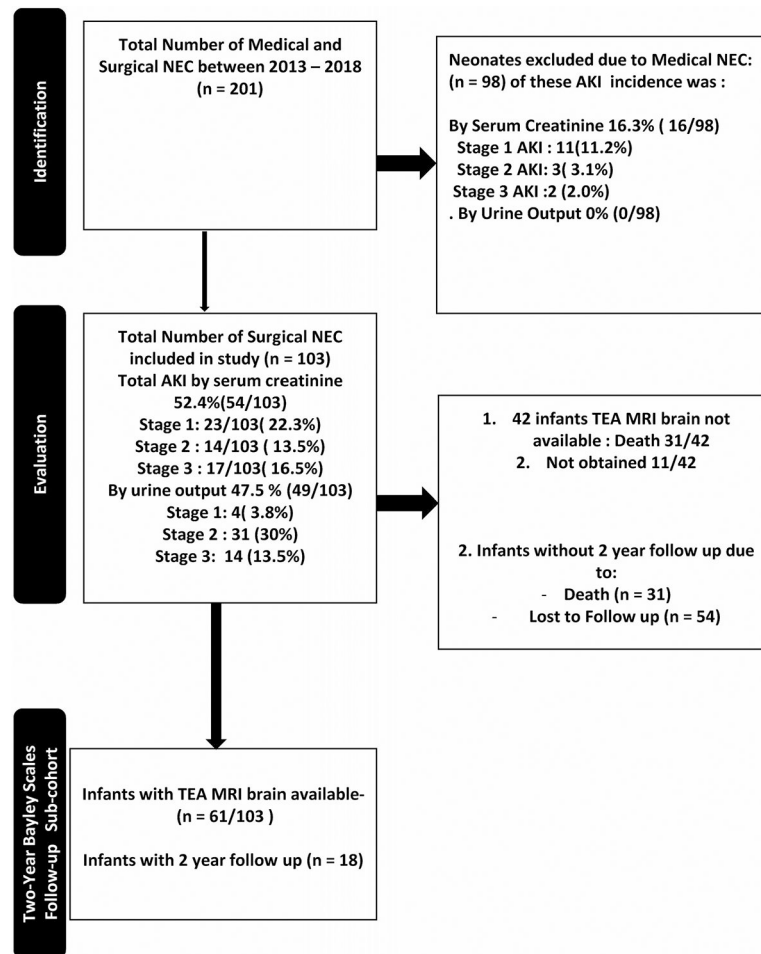


Figure 1.
Flow diagram showing the patient enrollment.

Table 1. Demographic and clinical features in neonates with Stage 2 and 3 AKI by both serum creatinine and urine output.

	N	Total N = 103	Severe AKI N = 60	Non-severe AKI N = 43	p Value
Prenatal information					
Pregnancy-Induced Hypertension, <i>n</i> (%)	103	29 (28.2%)	18 (30%)	11 (25.6%)	.623
Chronic Hypertension, <i>n</i> (%)	84	15 (17.9%)	8 (15.4%)	7 (21.9%)	.451
Chorioamnionitis, <i>n</i> (%)	102	10 (9.8%)	7 (11.9%)	3 (7%)	.513
Antenatal Steroids, <i>n</i> (%)	101	73 (72.3%)	45 (76.3%)	28 (66.7%)	.288
Infant demographics					
Gestational age (weeks), median (IQR)	103	26.4 (24.3, 29.6)	25.4 (24.3, 27.8)	27 (25, 32)	.069
Birth weight (grams), median (IQR)	103	780 (650, 1180)	715 (625, 990)	950 (690, 1600)	.023
Small for gestational age, <i>n</i> (%)	103	35 (34%)	21 (35.0%)	14 (32.6%)	.796
Gender (female), <i>n</i> (%)	103	36 (35%)	19 (31.7%)	17 (39.5%)	.409
Ethnicity, <i>n</i> (%)	103				.029
Caucasian		22 (21.4%)	9 (15%)	13 (30.2%)	
African American		77 (74.8%)	49 (81.7%)	28 (65.1%)	
Latino		2 (2%)	0 (0%)	2 (4.7%)	
Other		2 (2%)	2 (3.3%)	0 (0%)	
Mode of delivery, <i>n</i> (%)	103				.934
C-section		69 (67%)	40 (66.7%)	29 (67.4%)	
Vaginal		34 (33%)	20 (33.3%)	14 (32.6%)	
Apgar Score < 6 at 5 min, <i>n</i> (%)	101	30 (29.7%)	21 (35.6%)	9 (21.4%)	.125
Outborn, <i>n</i> (%)	103	63 (61.2%)	40 (66.7%)	23 (53.5%)	.176
Infant medical information prior to NEC					
Patent ductus arteriosus, <i>n</i> (%)	103	59 (57.3%)	33 (55.0%)	26 (60.5%)	.58
Patent ductus arteriosus, indomethacin treated, <i>n</i> (%)	102	12 (11.8%)	11 (18.3%)	1 (2.4%)	.014
Patent ductus arteriosus, surgically ligated, <i>n</i> (%)	103	5 (4.9%)	4 (6.7%)	1 (2.3%)	.397
Sepsis variables					
Central line present (days), median (IQR)	93	50 (29, 77)	57 (36.5, 86.5)	38 (24, 65)	.067
Positive blood culture sepsis, <i>n</i> (%)	103	32 (31.1%)	23 (38.3%)	9 (20.9%)	0.06
CRP on day of NEC onset, median (IQR)	89	4 (1.2, 8)	5.05 (1.9, 8.5)	2.6 (0.9, 6.7)	.153

	<i>N</i>	Total <i>N</i> = 103	Severe AKI <i>N</i> = 60	Non-severe AKI <i>N</i> = 43	<i>p</i> Value
CRP at 24 h after NEC onset, median (IQR)	80	8.5 (3.1, 19.4)	14.4 (6.4, 19.8)	4.8 (1.6, 13.4)	.005
CRP at 48 h after NEC onset, median (IQR)	66	14.9 (3.3, 21.9)	15.7 (6.7, 24.5)	4.4 (2.4, 19.8)	.012
CRP at 96 h after NEC onset, median (IQR)	69	7.3 (4.1, 15.6)	7.6 (4.6, 15.5)	4.9 (2.6, 16)	.27
CRP at 1 week after NEC onset, median (IQR)	67	5.3 (2.9, 8.3)	5.2 (2.9, 8.6)	5.3 (2.9, 7.5)	.958
CRP at 2 weeks after NEC Onset, median (IQR)	64	3.4 (1.8, 5.8)	4 (2.4, 5.8)	2.8 (1.4, 5.4)	.103
Cholestasis at NEC Onset, n (%)	101	65 (64.4%)	44 (73.3%)	21 (51.2%)	.023

NEC: necrotizing enterocolitis; AKI: acute kidney injury; CRP: C-reactive protein

Categorical variables are presented as count (column percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with AKI were evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate, otherwise Fisher's exact were used with low expected cell counts.

The bold value signifies the *p* value is less than 0.05.

Table 2.

AKI stages by serum creatinine and urine output using KDIGO classification.

		AKI by urine output				Total
		State 0	Stage 1	Stage 2	Stage 3	
AKI by creatinine	State 0	26 53.1%	3 6.1%	16 32.7%	4 8.2%	49
	Stage 1	14 60.9%	0 0	8 34.8%	1 4.4%	23
	Stage 2	5 35.7%	0 0	4 28.6%	5 35.7%	14
	Stage 3	9 52.9%	1 5.9%	3 17.7%	4 23.5%	17
	Total	54	4	31	14	103

Frequency and row percent are presented. Shadow area – infants with severe AKI (Stage 2 and 3).

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Table 3.

Features in neonates with Stage 2 and 3 AKI by both serum creatinine and urine output.

	Total cohort <i>n</i> = 103	Severe AKI <i>n</i> = 60	Non-severe AKI <i>n</i> = 43	<i>p</i> Value
Clinical presentation, <i>n</i> (%)	103			.036
Abdominal distension	92 (89.3%)	57 (95%)	35 (81.4%)	–
Bloody stools	8 (7.8%)	3 (5%)	5 (11.6%)	–
Feeding intolerance	3 (2.9%)	0 (0%)	3 (7%)	–
Radiological findings, <i>n</i> (%)	103			–
Pneumatisis	48 (46.6%)	31 (51.7%)	17 (39.5%)	.224
Pneumoperitoneum	55 (53.4%)	27 (45%)	28 (65.1%)	.044
Portal venous gas	8 (7.8%)	4 (6.7%)	4 (9.3%)	.717
Age of NEC onset (days), median (IQR)	103	14 (8, 23)	7 (4, 13)	.004
Fulminant NEC, <i>n</i> (%)	103	9 (15%)	10 (23.3%)	.287
Present of penrose drain, <i>n</i> (%)	98	41 (41.8%)	21 (52.5%)	.076
Surgery < 48 h, <i>n</i> (%)	103	71 (68.9%)	28 (65.1%)	.479
Length of bowel resected (cm), median (IQR)	101	12 (3.2, 28.8)	4.25 (2, 27.2)	.011
Region of bowel resected, <i>n</i> (%)	91			.040
Small bowel resected	58 (63.7%)	38 (66.7%)	20 (58.8%)	–
Large bowel resected	4 (4.4%)	0 (0%)	4 (11.8%)	–
Combined large and Small bowel resected	29 (31.9%)	19 (33.3%)	10 (29.4%)	–
Presence of Ileocecal valve, <i>n</i> (%)	102	73 (71.6%)	34 (81%)	.079
Surgical morbidity (infection, adhesions, strictures, dehiscence), <i>n</i> (%)	103	39 (37.9%)	25 (41.7%)	.347
Single surgical morbidity (infection, adhesions, strictures, dehiscence), <i>n</i> (%)	103	23 (22.3%)	15 (25%)	.442
More than one surgical morbidity (Infection, adhesions, strictures, dehiscence), <i>n</i> (%)	103	13 (12.6%)	8 (13.3%)	.797
Adhesions, <i>n</i> (%)	103	16 (15.5%)	10 (16.7%)	.708
Wound dehiscence, <i>n</i> (%)	103	16 (15.5%)	5 (11.6%)	.354
Wound infection, <i>n</i> (%)	103	7 (6.8%)	1 (2.3%)	.234
Stricture, <i>n</i> (%)	103	8 (7.8%)	3 (7%)	1
Fistula, <i>n</i> (%)	103	6 (5.8%)	5 (8.3%)	.397
Compartment syndrome, <i>n</i> (%)	103	2 (1.9%)	1 (2.3%)	1
Short bowel syndrome, <i>n</i> (%)	86	43 (50%)	13 (40.6%)	.181

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NEC: necrotizing enterocolitis; AKI: acute kidney injury

Categorical variables are presented as count (column percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with AKI were evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate; otherwise, Fisher's Exact was used with low expected cell counts.

The bold value signifies the p value is less than 0.05.

Table 4.

Postoperative features and outcomes in neonates with Stage 2 and 3 AKI by both serum creatinine and UOP.

	Total N = 103	Severe AKI N = 60	Non-severe AKI N = 43	p Value
Post-operative features and outcomes				
Post-operative Ileus days (days), median (IQR)	84	14 (12, 20)	9 (7, 14)	<.001
Post-operative day at starting enteral feedings (days), median (IQR)	83	15 (13, 23)	10 (8, 15)	<.001
Day of attainment of full enteral feedings (120 mL/kg), median (IQR)	69	75 (43, 109)	44.5 (26, 68.5)	.008
Duration of parenteral nutrition (days), median (IQR)	102	99 (56.5, 140)	70 (47, 114)	.078
Breast milk, n (%)	19 (18.5%)	4 (6.7%)	15 (34.9%)	<.001
Donor milk, n (%)	103	17 (28.3%)	6 (14%)	.084
Formula feeds, n (%)	103	52 (50.5%)	21 (48.8%)	.777
Breast milk and formula feeds, n (%)	103	17 (16.5%)	4 (9.3%)	.096
Post-operative systemic course				
Assisted ventilation (intubated), n (%)	100	88 (88%)	33 (78.6%)	.027
Intubated/invasive ventilation				
Non-invasive		7 (7%)	4 (9.5%)	–
High flow		3 (3%)	3 (7.1%)	–
CPAP		2 (2%)	2 (4.8%)	–
24 h Presser support, n (%)	80 (77.7%)	53 (88.3%)	27 (62.8%)	.002
Postnatal use of steroids, n (%)	60 (58.3%)	37 (61.7%)	23 (53.5%)	.407
Discharge				
Length of stay (days), median (IQR)	103	121 (72, 177)	140.5 (88, 180)	.028
Death, n (%)	103	32 (31.1%)	13 (30.2%)	.877

NEC: necrotizing enterocolitis; AKI: acute kidney injury

Categorical variables are presented as count (column percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. When the normality assumption was not satisfied, continuous measures' statistical associations with the Kruskal-Wallis Test. Differences in categorical measures' associations were tested using the Chi-square test when cell counts were adequate; otherwise, Fisher's Exact was used with low expected cell counts.

The bold value signifies the p value is less than 0.05.

Table 5.

Neurodevelopment outcomes in neonates with Stage 1–3 AKI by serum creatinine.

Variable	Total cohort <i>n</i> = 103	AKI by serum creatinine			<i>p</i> Value
		AKI present <i>n</i> = 54	AKI absent <i>n</i> = 49		
MRI corrected GA, median (IQR)	58	40.5 (38.3, 46.1)	40.4 (38.1, 46.1)	40.6 (38.3, 48.2)	.821
White matter injury present, <i>n</i> (%)	61	33 (54.1%)	18 (90.0%)	15 (36.6%)	<.001
White matter injury abnormality, <i>n</i> (%)	61	–	–	–	<.001
No abnormality (5–6)	–	28 (45.9%)	2 (10.0%)	26 (63.4%)	–
Mild (7–9)	–	15 (24.6%)	6 (30.0%)	9 (22.0%)	–
Moderate (10–12)	–	12 (19.7%)	9 (45.0%)	3 (7.3%)	–
Severe (13–15)	–	6 (9.8%)	3 (15.0%)	3 (7.3%)	–
Grey matter abnormality Composite score, <i>n</i> (%)	60				.432
Normal (3–5)	–	53 (88.3%)	27 (84.4%)	26 (92.9%)	–
Abnormal (6–9)	–	7 (11.7%)	5 (15.6%)	2 (7.1%)	–
Cerebellar injury, <i>n</i> (%)	57	19 (33.3%)	12 (40%)	7 (25.9%)	.260
ROP, <i>n</i> (%)	70	35 (50%)	23 (63.9%)	12 (35.3%)	.017
Long-term eye complications, <i>n</i> (%)	27				.778
Myopia	–	10 (37%)	7 (41.2%)	3 (30%)	–
Hyperopia	–	11 (40.7%)	7 (41.2%)	4 (40%)	–
Strabismus	–	6 (22.2%)	3 (17.7%)	3 (30%)	–

AKI: acute kidney injury.

Categorical variables are presented as count (column percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with AKI were evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate; otherwise, Fisher's Exact was used with low expected cell counts.

The bold value signifies the *p* value is less than 0.05.

Table 6.

Brain MRI findings in neonates with surgical NEC based on Stage 2 and 3 AKI by serum creatinine.

	Total cohort <i>n</i> = 103	Severe AKI <i>N</i> = 31	Non-severe AKI <i>N</i> = 72	<i>p</i> Value	
MRI corrected GA, median (IQR)	58	40.5 (38.3, 46.1)	39.2 (37.3, 49.1)	40.6 (39.1, 45.3)	.426
White matter injury present, <i>n</i> (%)	61	33 (54.1%)	18 (90%)	15 (36.6%)	<.001
White Matter Injury Abnormality, <i>n</i> (%)	61	—	—	—	<.001
No abnormality (5–6)	—	28 (45.9%)	2 (10%)	26 (63.4%)	—
Mild (7–9)	—	15 (24.6%)	6 (30%)	9 (22.0%)	—
Moderate (10–12)	—	12 (19.7%)	9 (45%)	3 (7.3%)	—
Severe (13–15)	—	6 (9.8%)	3 (15%)	3 (7.3%)	—
Grade of white matter signal abnormality nature and extent, <i>n</i> (%)	60	—	—	—	<.001
Normal	—	35 (58.3%)	4 (20%)	31 (77.5%)	—
Mild	—	12 (20%)	7 (35%)	5 (12.5%)	—
Moderate	—	13 (21.7%)	9 (45%)	4 (10%)	—
Loss in volume of periventricular white matter, <i>n</i> (%)	60	—	—	—	<.001
Grade 1	—	29 (48.3%)	3 (15%)	26 (65%)	—
Grade 2	—	25 (41.7%)	13 (65%)	12 (30%)	—
Grade 3	—	6 (10%)	4 (20%)	2 (5%)	—
Extent of cystic abnormality, <i>n</i> (%)	60	—	—	—	.039
Grade 1	—	45 (75%)	11 (55%)	34 (85%)	—
Grade 2	—	10 (16.7%)	6 (30%)	4 (10%)	—
Grade 3	—	5 (8.3%)	3 (15%)	2 (5%)	—
Ventricular dilation, <i>n</i> (%)	60	—	—	—	.001
Grade 1	—	29 (48.3%)	3 (15%)	26 (65%)	—
Grade 2	—	23 (38.3%)	13 (65%)	10 (25%)	—
Grade 3	—	8 (13.3%)	4 (20%)	4 (10%)	—
Thinning of corpus callosum, <i>n</i> (%)	60	—	—	—	.004
Grade 1	—	29 (48.3%)	4 (20%)	25 (62.5%)	—
Grade 2	—	24 (40%)	13 (65%)	11 (27.5%)	—
Grade 3	—	7 (11.7%)	3 (15%)	4 (10%)	—
Grey matter abnormality composite score, <i>n</i> (%)	60	—	—	—	.208

	Total cohort <i>n</i> = 103	Severe AKI <i>N</i> = 31	Non-severe AKI <i>N</i> = 72	<i>p</i> Value
Normal (3–5)	–	16 (80%)	37 (92.5%)	–
Abnormal (6–9)	–	4 (20%)	3 (7.5%)	–
Extent of grey matter signal abnormality, <i>n</i> (%)	59	–	–	.362
Grade 1	–	16 (80%)	35 (89.7%)	–
Grade 2	–	3 (15%)	3 (7.7%)	–
Grade 3	–	1 (5%)	1 (2.6%)	–
Quality of gyral maturation, <i>n</i> (%)	60	–	–	.145
Grade 1	–	15 (75%)	37 (92.5%)	–
Grade 2	–	4 (20%)	2 (5%)	–
Grade 3	–	1 (5%)	1 (2.5%)	–
Size of subarachnoid space, <i>n</i> (%)	59	–	–	.753
Grade 1	–	47 (79.7%)	32 (82.1%)	–
Grade 2	–	10 (17%)	6 (15.4%)	–
Grade 3	–	2 (3.4%)	1 (2.6%)	–
Cerebellar injury, <i>n</i> (%)	57	9 (50%)	10 (25.6%)	.070

AKI: acute kidney injury.

Categorical variables are presented as count (column percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with AKI are evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate; otherwise, Fisher's exact test was used with low expected cell counts.

The bold value signifies the *p* value is less than 0.05.

Table 7.

Factors associated with white matter brain injury on multivariable logistic regression analysis.

Variable	Factors associated with any white matter brain injury (present vs. absent)			Factor associations with Grade 3 or 4 white matter brain injury (present vs. absent)			Factor associations with white matter brain injury (ordinal levels)				
	Odds ratio	95% CI	<i>p</i>	Odds ratio	95% CI	<i>p</i>	Odds ratio	95% CI	<i>p</i>		
AKI by serum creatinine (Stage 2/3 vs. Stage 1 or normal)	12.9	0.7	241	0.087	9.8	0.8	116	6.2	1.1	35.5	.041
Indomethacin use (vs. not use)	0.5	0.1	12.9	0.706	2.1	0.1	46.2	0.6	0.1	4.9	.666
Birth weight (g)	6.7	1.0	44.5	0.092	3.6	0.5	44.5	3.6	1.0	12.6	.072
Length of bowel resected (cm)	0.5	0.06	4.8	0.562	0.6	0.1	4.8	0.4	0.1	1.8	.251
Post-operative days at starting enteral feedings (days)	2.8	0.5	15.7	0.240	4.8	0.9	25.3	2.6	0.8	8.3	.097
Day of attainment of full enteral feedings (120 mL/kg)	1.6	0.5	5.2	0.386	1.7	0.5	5.9	1.8	0.9	3.8	.112
24 h Pressor support, <i>n</i> (%)	35.8	0.7	>999.9	0.073	5.0	0.1	210	15.9	1.1	231	.043
CRP at 24 h after NEC onset	0.8	0.2	3.2	0.766	0.5	0.1	1.7	0.9	0.4	2.2	.835
Age of NEC onset (days)	1.2	0.4	3.8	0.766	3.1	0.9	10.4	1.3	0.6	2.8	.544
Length of stay (days)	4.9	0.7	35.6	0.100	3.5	0.5	25.7	3.3	1.0	9.6	.042

Odds ratio for continuous variables are expressed per standard deviation of that factor.

The bold value signifies the *p* value is less than 0.05.