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The Impact of Increased Awareness of Acute Kidney Injury in the Neonatal Intensive Care Unit on Acute Kidney Injury Incidence and Reporting: Results of a Retrospective Cohort Study

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Abstract

Objective: To evaluate the impact of nephrology integration in the NICU on acute kidney injury (AKI) incidence, provider reporting, and nephrology referral.

Study Design: Cohort study in a single-center NICU from January 2012 to December 2017 (n=1464). We assessed the impact of clinical practice changes including neonatal-nephrology rounds on the incidence of AKI.

Results: AKI occurred in 318 neonates (22%). AKI occurred less frequently in those admitted after clinical practice changes (P<.001). After multivariable adjustment, clinical practice changes were associated with reduced odds of AKI (adjusted odds ratio, 0.31;95% CI 0.22–0.44, P<.001).

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Author Contributions

MS and AK conceptualized and designed the study, collected data, carried out the initial analysis, drafted the initial manuscript, and reviewed and revised the manuscript. JL and TL conceptualized and designed the study and reviewed and revised the manuscript. SM assisted with data analysis, and reviewed and revised the manuscript. AP carried out the analysis, and reviewed and revised the manuscript. SC and SH supervised the conceptualization and design of the study and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare no competing financial interests in relation to the work described.

Ethics Approval and Consent to Participate

The Institutional Review Boards at the University of Washington and Seattle Children's Hospital approved the study protocol.

Availability of Data and Materials

Data is available upon request.

Provider reporting of AKI improved ($P < .001$) and more neonates were referred for nephrology follow-up ($P < .001$).

Conclusions: Increased nephrology integration in the NICU was associated with decreased AKI incidence. While recognition of AKI improved, AKI remained poorly reported and nephrology AKI follow-up did not routinely occur. This study supports the importance of increased nephrology involvement in the NICU.

Introduction

Acute kidney injury (AKI) is common in pediatric patients, occurring in critically-ill children of all ages.¹ AKI occurs in up to 30% of high-risk neonates admitted to the Neonatal Intensive Care Unit (NICU)²⁻⁴ and rates are even higher in very low birth weight (VLBW) neonates, term neonates with hypoxic ischemic encephalopathy, those on extracorporeal membrane oxygenation, and neonates undergoing cardiac surgery.⁵⁻⁸ Studies consistently show neonatal AKI is common and associated with poor outcomes, including a higher risk of death, longer hospitalization and more complicated hospital stay.^{2,8}

Neonates admitted to the intensive care unit may be inherently at increased risk of chronic kidney disease (CKD). In those born prematurely, this risk comes from shortened nephrogenesis, resulting in a lower nephron mass.⁹⁻¹¹ Children who survive an episode of AKI are at increased risk for repeated episodes of AKI as well as CKD.^{9,14,15} Premature neonates may also be at increased risk of developing CKD as a sequelae of AKI due to their decreased nephron mass.^{12,13} Children surviving an episode of AKI should have long-term follow-up for monitoring of their kidney function. Clinical practice guidelines recommend that all patients with AKI be evaluated 3–6 months following their kidney injury to assess for onset or worsening of CKD.¹⁶

Unfortunately, the diagnosis of neonatal AKI remains under-recognized, made in only 10–30% of neonates with AKI.^{5,17} Without a formal diagnosis, many neonates are not identified for long-term follow up, reducing providers ability to identify CKD early. We sought to evaluate the impact of clinical practice changes instituted to increase AKI awareness in the NICU on AKI incidence, provider recognition of AKI, and nephrology referral rates. We hypothesized that increasing awareness of AKI in the NICU would improve provider reporting of AKI and referral to nephrology for these high-risk neonates.

Subjects and Methods

Patient Population

We included all neonates admitted to the University of Washington Medical Center's Level 3 neonatal intensive care unit (NICU) from January 1, 2012, to December 31, 2017.

Neonates who died, were discharged, or were transferred to other institutions within 72 hours were excluded. Additionally, patients admitted after 2 days of age were excluded, as laboratory data prior to transfer were often inaccessible. The Institutional Review Boards at the University of Washington and Seattle Children's Hospital approved the study protocol.

Clinical Practice Changes to Increase Nephrology Integration

Starting in 2015, several clinical practice changes were made in order to improve care for neonates with AKI in the NICU at University of Washington Medical Center. A dedicated twice monthly AKI follow-up clinic was started in January 2015. This clinic provides a focused space for teaching and education for patients following AKI. In the NICU, additional provider education on diagnosis and importance of AKI was initiated. This included presentations at resident teaching conference, monthly resident didactic teaching, and education of neonatologists during monthly meetings and by reminder email. Finally, weekly “Neonatal Nephrology” rounds were started in January 2016 in which a nephrologist joined the NICU work rounds to collaboratively discuss neonates with AKI, assist with diagnosis of AKI, and make recommendations for follow-up care when appropriate (Figure 1).

Data Collection and AKI Diagnosis

Data were collected from the electronic medical record (EMR) for each patient from admission until hospital discharge, and included demographics, gestational age, birth weight, Apgar scores, laboratory results, medications received, length of stay, mortality, and follow-up appointments that were made at the time of NICU discharge. Neonates were classified as small, appropriate, or large for gestational age using reference standards.¹⁸ Nephrotoxin exposure was based on medication recorded within the EMR. Nephrotoxic medications considered for this analysis were acyclovir, amphotericin, gentamicin, indomethacin, ibuprofen, piperacillin-tazobactam, and vancomycin. Similar to other previous studies assessing nephrotoxin exposure in neonates, neonates who received 3 or more concurrent nephrotoxic medications during their admission were considered to have high nephrotoxin exposure.¹⁹ We did not consider a prolonged single nephrotoxin exposure as high nephrotoxin exposure.¹⁹

The cohort was divided into two groups of patients: cohort 1 – neonates admitted between January 1, 2012 and December 31, 2014, prior to the implementation of these clinical practice change measures and cohort 2 – neonates admitted between January 1, 2015 and December 31, 2017, following the initiation of these measures. Of note, patients were born in Cohort 1 that remained admitted during Cohort 2 were excluded from this analysis.

AKI was classified using the modified KDIGO definitions previously used in neonates (Supplemental Table 1).^{15,20} Urine output criteria were not used. For patients with multiple episodes of AKI, the highest stage of AKI reached was used for analysis. In those neonates with AKI, we assessed provider reporting of AKI. A neonate was considered to have provider reported AKI if any diagnosis or characterization in the discharge summary would have alerted a medical provider reading to the presence of AKI, regardless of whether the term AKI was used. For example, a neonate diagnosed with acute renal failure, azotemia, or elevated creatinine were all considered to have provider reported AKI. Discharge summaries which did not include any statements describing AKI were classified as having not reported AKI in the discharge summary. Nephrology referral was determined if the patient was scheduled for follow-up or plan for nephrology referral specifically for AKI was discussed in the discharge summary.

Statistical Analysis

Categorical variables were compared using chi-square or Fisher exact tests, and continuous variables were compared using Student t-testing and Mann-Whitney U tests as appropriate. Associations between the cohorts and the binary outcome of AKI was investigated using logistic regression. Factors considered confounding were specified in each model as covariates and were determined *a priori*. These included ethnicity, race, gestational age, twin gestation, 5-minute APGAR score, very low birth weight, high nephrotoxic medication exposure, small for gestational age, and number of creatinine values obtained during admission. Number of creatinine values obtained was assessed both as a proxy marker of clinical illness severity, and also as a marker of increased provider awareness of kidney function. Reported statistics for these models include the adjusted odds ratio and corresponding 95% confidence interval (CI). A two-sided significance level of 0.05 was used for all tests. Statistical analyses were performed using SPSS Statistics, version 25 (IBM, Armonk, New York) and logistic regression was performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Demographic Characteristics

In total, 2,733 neonates were admitted to the NICU from January 1, 2012 to December 31, 2017. Of these, 679 were removed from the analysis for having at least one of the following exclusions: admission >2 days of age, discharge or transfer within 72 hours of admission, admission spanning both cohort 1 and 2, or insufficient (1) serum creatinine measurements. The remaining 1,464 neonates were included in the analysis. Of these, 666 neonates (45%) were admitted prior to January 1, 2015 and were included in cohort 1. There were 798 neonates (55%) born on or after January 1, 2015, which comprised cohort 2 (Figure 2).

Neonates in cohort 1 were more likely to be born at lower gestational ages, and to have higher 1- and 5-minute Apgar scores than those in cohort 2 (Table 1). Neonates in cohort 1 were more likely to be born small for gestational age or very-low birth weight. When comparing neonates with AKI in cohort 1 to those with AKI in cohort 2, neonates in cohort 1 had a higher 1- and 5-minute Apgar scores. No other baseline differences were observed between patients with AKI in either cohort. There was no difference in survival rates between cohorts.

Neonates in Cohort 2 were less likely to receive Gentamicin (56% versus 64%, $P=.002$) or NSAIDs (3% versus 12%, $P<.001$) than those in Cohort 1. Neonates in Cohort 2 were less likely to receive 3 or more nephrotoxic medications (8% versus 12%, $P=.011$). There was no difference in the percentage of neonates receiving other assessed nephrotoxic medications. (Supplemental Table 2)

Acute Kidney Injury and Outcomes

AKI occurred in 318 of 1464 (22%) neonates. Of those neonates with AKI, 211 (66%) reached Stage 1 AKI, 84 (26%) reached Stage 2, and 23 (7%) reached Stage 3 (Table 2). Neonates with AKI were more likely to be Hispanic (24% versus 16%, $P=.002$) and

Caucasian (79% versus 73%, $P<.001$) than those without AKI. Those with AKI were less likely to be born following twin gestation (18% versus 24%, $P=.024$). Infants with AKI were more likely to be born at lower gestational ages (mean of 28 weeks versus 33 weeks, $P=.027$). Neonates with AKI were more likely to have longer lengths of stay than those without AKI (mean of 70 days versus 38 days, $P<.001$), and were more likely to die during their NICU admission (10% versus 0.6%, $P<.001$). Neonates with AKI were also more likely to receive nephrotoxic medications compared to those without AKI (Supplemental Table 2).

Clinical Practice Changes and Acute Kidney Injury

In cohort 1, 30% ($n=201$) neonates experienced AKI. This was significantly higher than the 15% ($n=117$) of neonates that had AKI in cohort 2. The distribution of AKI stage was different between cohort 1 and cohort 2, with neonates in cohort 2 more likely to have lower stages of AKI ($P<.001$) (Table 2).

Increased nephrology integration in the NICU (summarized in Figure 1) was associated with a decreased risk of AKI (adjusted odds ratio 0.31, 95% confidence interval 0.22–0.44, $P<.001$), after controlling for cohort differences, nephrotoxin exposure, and AKI risk factors (Table 3). While AKI was associated with high nephrotoxin utilization in both the univariable and multivariable model (adjusted odds ratio 2.04, 95% confidence interval 1.20–3.46, $P<.001$); this alone did not account for the decreased AKI incidence.

Acute Kidney Injury Reporting and Nephrology Referral

Only 9% of AKI was reported by neonatology providers prior to the intervention (cohort 1). This increased to 23% of AKI being reported by providers in the discharge summary ($P<.001$) in Cohort 2. There were significant improvements in provider reporting of Stage 1 AKI from 2% to 11% ($P=.007$) and Stage 2 AKI from 13% to 43% ($P=.002$). No change was seen in the reporting of Stage 3 AKI (Table 2).

We found no difference in the rate of inpatient nephrology consultation, however the rate of referral to outpatient nephrology for AKI increased. Only 1 of 184 (0.01%) surviving patients with AKI in cohort 1 had an outpatient nephrology referral made, compared with 9 of 103 (8.7%) in cohort 2. All of the patients referred for AKI follow-up had either Stage 2 or Stage 3 AKI.

Discussion

In this study, we found that clinical practice changes designed to increase awareness of AKI in the NICU were associated with increased AKI reporting by providers, decreased AKI incidence, and increased outpatient referrals for neonates with AKI. Although similarities exist with previous studies which sought to increase diagnosis and referral of neonates following neonatal AKI through standardized guidelines of care,²¹ we additionally show decreased AKI incidence following increased education including integration of nephrology providers into “Neonatal Nephrology” rounds.

We report a baseline AKI recognition rate approximately 10%, lower than that described in prior studies (12–35%).^{5,17} We hypothesize that this may have been due to lack of awareness of the diagnostic criteria or of the clinical implications of neonatal AKI. We found similar rates of nephrology referral to previous studies at baseline (<1%).⁵ Neonates with Stage 1 and Stage 2 AKI were more likely to be recognized by providers as having AKI following clinical practice changes. Improvement in recognition of Stage 3 AKI was not observed, which may be due to the fact that Stage 3 AKI is often less subtle with more dramatic changes in urine output and serum creatinine and is often more easily recognized. Additionally, our sample size for patients with Stage 3 AKI was small, which makes recognition of improvement challenging. There was no increase in nephrology consultation, which we suspect was due to Neonatal Nephrology rounds, as a nephrology provider was available to answer questions on a weekly basis.

There was a significant decrease in the incidence of AKI which remained after controlling for differences between cohorts and factors which may impact AKI development. While there were changes in the demographic characteristics of patients admitted between the two cohorts (e.g. more VLBW infants in cohort 2), these differences were accounted for in multivariable modeling, suggesting that the difference in AKI is independent of these factors. There are several possible reasons for the decreased AKI rate. Implementation of this practice change intervention may have increased awareness of aspects of clinical care which might impact kidney health.²² Provider education may have increased recognition of AKI risk factors and changed provider practice. For example, we saw a decrease of gentamicin use from Cohort 1 to Cohort 2. This may reflect provider awareness of AKI and avoidance of nephrotoxin exposure, resulting in decreased nephrotoxin-associated AKI. Gentamicin avoidance in particular may reflect increased antibiotic stewardship in the NICU, however our data set did not capture other antibiotic use to serve as a control. There were no changes in standard antibiotic treatment, the number of serum creatinine values obtained, or other changes in neonatology practice which would account for such a change. Other changes in NICU practice such as first line therapy for PDA treatment shifting from NSAID to acetaminophen over the course of the study may have contributed to this decrease in AKI incidence. However, the persistence of the association between AKI incidence and our clinical practice changes in multivariable modeling after accounting for nephrotoxin exposure suggests that the effect is in part due to the clinical practice change alone.

These findings align with recently published studies describing both the poor baseline recognition of neonatal AKI as well as improvement following implementation of guidelines targeting recognition of AKI.^{5,17} The integration of pediatric nephrology providers into neonatal intensive care units improves the recognition of AKI and management of kidney related complications, and increases follow-up of patients at high risk for future CKD.^{21,23} The importance of neonatal-nephrology integration is especially valuable in the NICU where diagnosis of AKI is challenging due to slow neonatal maturation of glomerular filtration rate, maternal creatinine, and poor biomarkers of kidney dysfunction.^{20,24} Additionally, an episode of AKI in the NICU is an opportunity to identify and monitor a patient at high risk of developing CKD.^{9,10} Further long-term studies of infants with AKI are needed to develop consensus guidelines for follow-up in this population.

A Neonatal Nephrology program emphasizes early referral to nephrology clinic and facilitates discussion of kidney health monitoring, early identification of CKD, and risk reduction. Early identification of pediatric patients with CKD is essential to slow progression of kidney disease as it allows initiation of treatment to improve kidney function into adulthood.

Our findings further expand recent work focused on reducing nephrotoxin associated acute kidney injury through improved surveillance and monitoring, further supporting the importance of integration of nephrology providers into intensive care units.¹⁹ While such “Neonatal Nephrology” integration is both time and resource intensive, we show that it is associated with decreased AKI incidence, improved recognition, and increased follow-up for neonates with kidney injury and it may have the potential to improve care. Despite an increase in identification of AKI and referral for AKI follow-up, the uptake of these interventions remained below expected interval improvement with clinical practice changes. The reasons for this limited uptake could include frequency of integrated rounding or the lack of consensus guidelines for follow-up of these infants. Additionally, collaboration of nephrology providers with critical care medicine may be a challenge due to workforce limitations.²⁵ Qualitative study of integrated rounds should be performed to assess these interventions (e.g. workload, clinical utility by neonatology team, cost savings) to establish if these practices may actually save time in addition to improving clinical care.

There are several important limitations of this study. We used the neonatal modification of the KDIGO definitions for diagnosis of AKI.^{21,26} While we acknowledge the limitations of serum creatinine in this patient population, the most recent National Institute of Health (NIH) workshop on neonatal AKI provided expert guidance that this remains the best assessment of neonatal AKI.²⁷ Secondly, we did not assess oliguria, which increases the sensitivity of AKI classification in this patient population and may have identified additional neonates with impairments in kidney function.^{2,3} Third, we were unable to assess the temporal relationship between nephrotoxin exposure and AKI diagnosis due to limitations of the data. Additionally, given our study design, if a patient had more than one episode of AKI and only one was recognized by providers, a patient would be considered appropriately identified even though a second episode of AKI was not documented. Despite these limitations, this study has several strengths including a relatively large cohort and the use of up-to-date guidelines for diagnosis of AKI. While our work represents only a single center experience, our interventions, including the integration of a nephrology provider in the NICU, can be incorporated into clinical care at other institutions.

In conclusion, in this large single-center retrospective cohort, provider reporting of AKI increased, outpatient nephrology follow-up improved, and AKI incidence declined following clinical practice changes in the NICU. However, much progress remains to be made in improving AKI diagnosis and follow-up in this high-risk patient population. Further collaborative work by both nephrologists and neonatologists, such as multidisciplinary “Neonatal Nephrology” rounds and ongoing education, are needed to improve multidisciplinary care and improved recognition and follow-up of AKI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AKI Follow-Up Clinic

- Twice Monthly Clinic
- Staffed by 2 Pediatric Nephrologists
- Provided Hospital Follow-Up for Neonatal and Pediatric Patients with Identified AKI



Provider Education

- Scheduled Monthly Educational Didactics for trainees rotating in Neonatal ICU
- Covered AKI diagnosis, management and importance of AKI recognition



Neonatal Nephrology Rounds

- Weekly integrated rounds in NICU with Nephrologist
- Provided collaborative discussions on neonates with AKI
- Assisted with diagnosis and made recommendations for follow-up

Figure 1.
Clinical Practice Changes Instituted in 2015

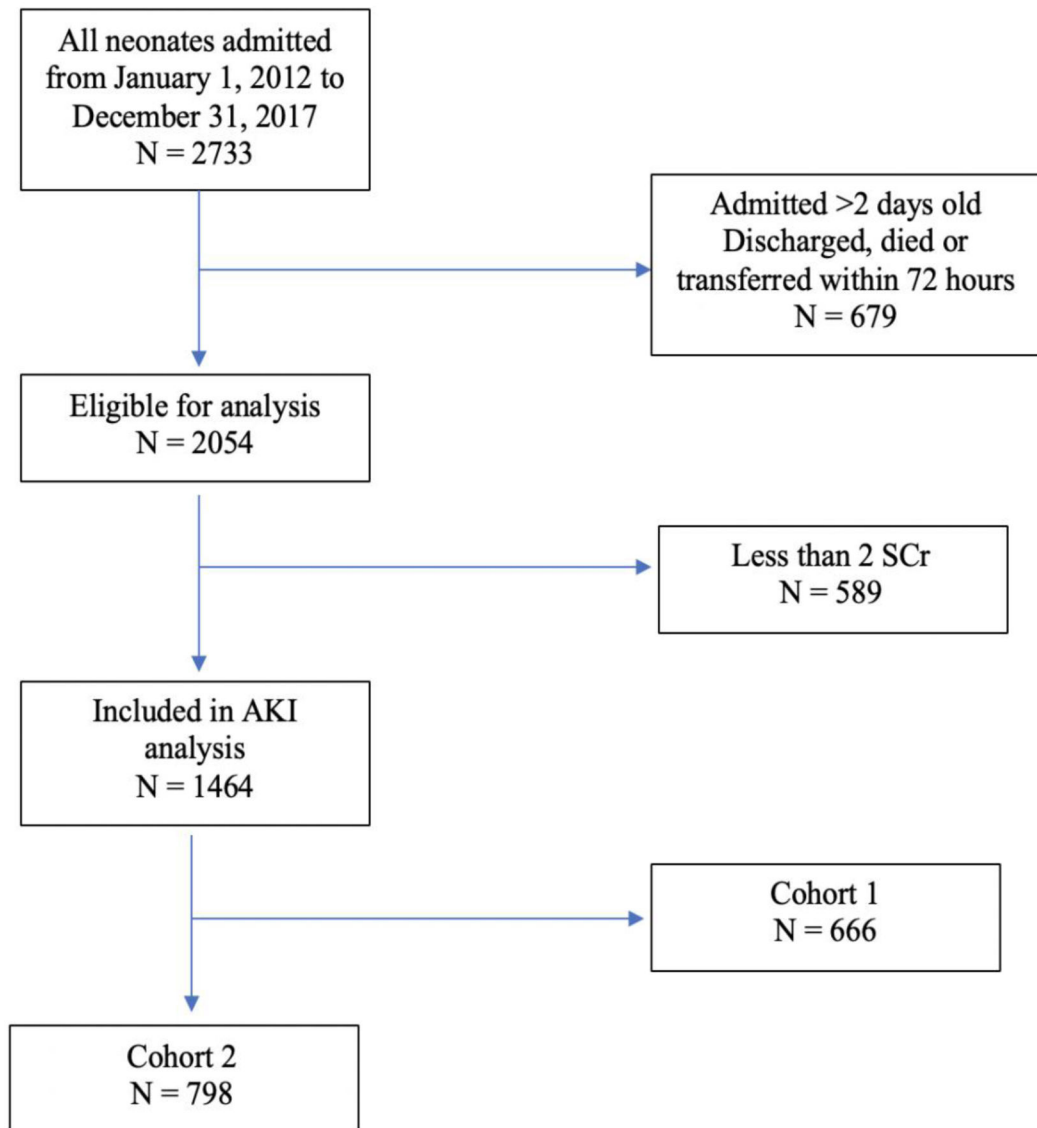


Figure 2.
Identification, exclusion and analysis of neonates for this study

Table 1.

Baseline Demographic Characteristics for neonates in Cohort 1 and Cohort 2

Characteristic	Cohort 1		Cohort 2	
	Total (n=666)	AKI (n=201)	Total (n=798)	AKI (n=117)
Sex (male)	364 (54.7%)	109 (54.2%)	419 (52.5%)	63 (53.8%)
Ethnicity				
Hispanic	120 (18.0%)	45 (22.4%)	140 (17.5%)	30 (25.6%)
Non-Hispanic	546 (82.0%)	156 (77.6%)	644 (80.7%)	87 (74.4%)
Unknown	0	0	14 (1.8%)	0
Race				
Caucasian	501 (75.2%)	160 (79.6%)	589 (73.8%)	92 (78.6%)
African-American	91 (13.7%)	25 (12.4%)	91 (11.4%)	14 (12.0%)
Asian	42 (6.3%)	8 (4.0%)	61 (7.6%)	5 (4.3%)
Other	32 (4.8%)	8 (4.0%)	42 (5.3%)	6 (5.1%)
Unknown	0	0	15 (1.9%)	0
Twin Gestation	149 (22.4%)	34 (16.9%)	182 (22.8%)	23 (19.7%)
Gestational Age				
22–29 weeks	214 (32.1%)	139 (69.2%)	198 (24.8%)	91 (77.8%)
29–36 weeks	328 (49.2%)	47 (23.4%)	459 (57.5%)	15 (12.8%)
>36 weeks	124 (18.6%)	15 (7.5%)	141 (17.7%)	11 (9.4%)
Birth Weight (kg)	1.7 (1.0–2.4)	1.1 (0.7–1.8)	1.81 (1.2–2.6)	1.1 (0.6–1.9)
1-Min Apgar (score)	4 (2, 5)	4 (3, 5)	5 (3, 7)	3 (2, 5)
5-Min Apgar (score)	7 (5, 8)	6 (4, 7)	7 (6, 8)	5 (3, 7)
Mode of Delivery				
Vaginal Delivery	175 (26.3%)	53 (26.4%)	222 (27.8%)	34 (29.1%)
C-Section	490 (73.8%)	148 (73.6%)	573 (71.8%)	83 (70.9%)
Unknown	1 (0.2%)	0	3 (0.4%)	0
SGA	134 (20.1%)	43 (21.4%)	125 (15.7%)	22 (18.8%)
VLBW	321 (48.2%)	159 (79.1%)	341 (42.7%)	99 (84.6%)
Mortality	21 (3.2%)	17 (8.5%)	17 (2.1%)	14 (12.0%)

AKI, Acute kidney injury; SGA, Small for Gestational Age; VLBW, Very Low Birth Weight;

Table 2.

AKI Incidence and Provider Recognition Between Cohort 1 and Cohort 2

	Cohort 1 (n=666)	Cohort 2 (n=798)	<i>p</i> value
AKI			
Overall	201 (30.2%)	117 (14.7%)	<.001
Stage 1	130 (64.7%)	81 (69.2%)	<.001
Stage 2	56 (28.9%)	28 (23.9%)	<.001
Stage 3	15 (7.5%)	8 (6.8%)	.062
AKI Recognition			
Overall	18 (9.0%)	27 (23.1%)	<.001
Stage 1	3 (2.3%)	8 (10.0%)	.007
Stage 2	7 (12.5%)	12 (42.9%)	.002
Stage 3	8 (53.3%)	7 (78%)	.31
Nephrology Consult	3 (0.5%)	4 (0.5%)	.99
Nephrology Outpatient Follow-up	1 (0.01%)	9 (8.7%)	<.001

AKI, Acute Kidney Injury

Table 3.Crude and Adjusted Odds Ratios¹ for Acute Kidney Injury During Study Period

	Unadjusted OR (95% CI)	<i>p</i> -Value	Adjusted ² OR (95% CI)	<i>p</i> -Value
Gestational Age		<0.001		<.001
36 – 42 weeks (reference)	1.00		1.00	
29 – 35 weeks	0.79 (0.49, 1.27)	0.327	0.71 (0.41, 1.26)	.24
22 – 29 weeks	11.62 (7.41, 18.20)	<0.001	2.18 (1.00, 4.74)	.051
Increased Nephrology Integration	0.40 (0.31, 0.51)	<0.001	0.31 (0.22, 0.44)	<.001
5-minute APGAR Score	0.68 (0.64, 0.73)	<0.001	0.80 (0.74, 0.88)	<.001
Number of Creatinine Values	1.13 (1.11, 1.14)	<0.001	1.08 (1.06, 1.10)	<.001
3 or more nephrotoxins³	15.86 (10.58, 23.78)	<0.001	2.04 (1.20, 3.46)	.009

AKI, Acute Kidney Injury; NICU, Neonatal Intensive Care Unit

¹Estimated from logistic regression²Adjusted for ethnicity, race, gestational age, twin gestation, higher 5-minute APGAR score, very low birth weight, high nephrotoxic medication exposure, small for gestational age, increased nephrology integration, and higher number of creatinine values obtained during admission.³Nephrotoxic medications considered for this analysis were acyclovir, amphotericin, gentamicin, indomethacin, ibuprofen, piperacillin-tazobactam, and vancomycin.