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Premature infants are more likely to survive at earlier gestational ages today than ever before. However, many of these infants face long-term complications associated with their prematurity, as their organs have not had sufficient time to develop. This is particularly notable in the kidney and the lung. Due to physiological similarities, injury of one of these systems can lead to the injury of another, a phenomenon known as kidney-lung crosstalk. Furthermore, infants who experience acute kidney injury are also at increased risk of experiencing chronic kidney disease in the future. Therefore, early identification and management of kidney and lung injuries is key for effective prevention of future chronic disease. This study addresses the frequency of kidney disease in a population of neonates with bronchopulmonary dysplasia, a chronic lung disease which is common in premature neonates.

PREDICTORS OF CHRONIC KIDNEY DISEASE DURING CHILDHOOD IN NEONATES WITH BRONCHOPULMONARY DYSPLASIA

CAPSTONE PROJECT REPORT

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CHAPTER I

INTRODUCTION

Prematurely born infants, born at less than thirty-seven weeks' gestational age, are more likely to survive at earlier gestational ages than ever before. In fact, the rates of preterm births have increased in past years while rates of mortality have declined.[1] Advances in medical research and technology as well as modern neonatal and pediatric care have allowed for over 95% of infants born at thirty-seven weeks gestation or earlier to survive into adulthood.[2] Specifically, these developments have allowed physicians to broaden their focus from greatly reducing rates of mortality among this vulnerable population to treating the comorbidities associated with preterm birth. Therapies aimed to help preterm infants such as corticosteroids, antibiotics, and tocolytic agents on top of technologies like supplemental oxygen or ventilation, extracorporeal membrane oxygenation (ECMO), and even bilirubin lights have enhanced physicians' abilities to target and treat conditions associated with prematurity.

Despite these advances, however, many individuals born preterm experience chronic disorders and complications as a result of their prematurity. Premature infants are two times more likely to have congenital defects than their full-term counterparts and can face a lifetime of treatments, surgeries, or therapies to remedy these ailments. Furthermore, the treatments these infants receive in the intensive care setting place additional strain on the body and can further induce multi-organ damage. This hospitalization may predispose infants to increased chronic

disease and range from outpatient management by primary care physicians to recurrent inpatient hospitalizations for persistent chronic issues. Thus, while mortality rates have dropped in recent years, comorbidities can incur a high cost for these vulnerable patients.

As medical technology continues to develop, it is imperative that physicians consider ways in which treatments can be optimized to tend to the patient in the most effective way possible while minimizing the comorbidities and complications associated with preterm birth. The present study will look at an example of this issue, in which renal health is inadvertently compromised by treatments and difficulties encountered in the neonatal intensive care setting every day.

CHAPTER II

BACKGROUND

The development of the kidneys begins by nine weeks of gestation and is completed by approximately thirty-six weeks' gestation.[3] Furthermore, the majority of nephrogenesis occurs during the third trimester of pregnancy; approximately sixty percent of the nephrons are generated during this time period.[4] Therefore, the last weeks of gestation are an especially crucial time for kidney development. Infants that are born preterm, or before thirty-seven weeks' completed gestation, are born with premature kidneys that did not have time to adequately develop in utero. To further complicate this issue, nephrons do not have the ability to regenerate themselves, so preterm infants are born with lower glomerular mass and fewer, immature nephrons and must work with this deficit for their whole lives.[5]

Most premature infants experience time in the neonatal intensive care unit (NICU), where they are given the medical attention, resources, and treatment needed for their vital signs and symptoms to stabilize to a healthy, viable baseline level. While significant advances have been made over the years in the technology and treatment of most outcomes associated with preterm birth, kidney outcomes are sometimes overlooked or even compromised when treating for other conditions. For example, non-steroidal anti-inflammatory drugs (NSAIDs) are frequently needed to treat the heart defect patent ductus arteriosus (PDA), but NSAIDs inhibit the enzyme cyclooxygenase, which moderates renal vascular tone.[6] Antibiotics such as ampicillin and

gentamicin are commonly administered in the NICU to treat bacterial infections that could lead to sepsis; however, these antibiotics are excreted in the urine so can collect in the immature kidney, leading to tubular damage.[6] In the context of the NICU, it is imperative physicians are mindful of the nephrotoxic burden that several commonly administered medications carry in order to minimize renal injury as much as possible for the already-underdeveloped kidneys of preterm infants.

Injury to the kidneys is quantifiable and has recently assumed a more uniform definition in healthcare. Formerly termed acute renal failure, acute kidney injury (AKI) is an episode where the kidneys experience a partial or complete loss in their function. The criteria for an AKI episode have evolved over the years, but most researchers and physicians have now adopted the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury.[7] According to KDIGO guidelines, an AKI episode occurs when either an individual's serum creatinine (SCr) level rises by at least 0.3 mg/dL, the SCr level rises by 1.5 times the baseline (considered as the lowest SCr level within the past seven days), or the individual's urine output (UOP) is less than 0.5 mL/kg/h for six hours. If the SCr level experiences greater rise, or if the individual has more dramatic decrease in UOP, the AKI stage increases incrementally (see TABLE 1 for AKI staging according to KDIGO guidelines). Both the increase in SCr and decrease in UOP are direct reflections of impairment in kidney function, specifically in the kidney's ability to filter the blood for waste products.[7] Of note, cystatin C is an additional biomarker used to measure kidney function and predict an AKI event. It does not exhibit any significant protein binding and is freely filtered by the glomeruli of the kidney, making it an excellent marker for kidney function.[8, 9] In some cases, it may provide a more

accurate depiction of glomerular filtration rate than SCr, especially in patients with low muscle mass or fluid overload, both of which are common in premature infants.[9]

TABLE 1. Acute Kidney Injury Staging According to KDIGO Guidelines

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥0.3 mg/dL increase	<0.5 mL/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 mL/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in SCr to ≥4.0 mg/dL OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 hours OR Anuria for ≥12 hours

SCr, serum creatinine; eGFR, estimated glomerular filtration rate

Several studies have evaluated the risk factors and outcomes of AKI. Perinatal risk factors such as lower gestational age and low birth weight have demonstrated an inverse association with AKI occurrence. Infants who are born before thirty-two weeks' gestation have been shown to have nearly double the risk of AKI,[10] and AKI incidence has been observed to increase significantly in extremely low birth weight infants.[11] Many postnatal factors have also been observed to increase neonatal AKI risk. Nephrotoxic medications, as mentioned previously, are often administered in the NICU setting for other comorbidities given the high rates of infection found in the intensive care setting.[6] Other medical comorbidities that are the result of preterm birth or NICU admission can also increase AKI incidence due to the redirection of cardiac output away from the kidneys to other organs that often occurs.[12] One example of this is

hypoxic-ischemic encephalopathy (HIE). A 2021 study of infants with HIE found that 70% of stage III infants experienced an episode of AKI.[13] As for outcomes of neonatal AKI, many studies have focused on the effects of AKI on both neonatal course and hospital admission outcomes. Mortality rates for infants with neonatal AKI are higher than those without AKI, with likelihood doubling with an early AKI episode.[14] Neonatal AKI incidence has also demonstrated a correlation with the length of hospital admission, adding up to one and a half weeks of time onto the hospital visit.[14, 15]

With careful monitoring and observation, neonatal AKI can be predicted or even potentially reduced in severity. In an inpatient setting, monitoring for neonatal AKI includes considering the infant's complete birth and medical history, closely monitoring fluid intake and output and overall clinical fluid balance, and carefully selecting which medications are administered. It also includes tracking laboratory values, namely SCr and cystatin C levels,[16] which allows for better approximation of kidney function, when an episode of AKI might occur, as well as when one has already taken place. Several studies have found that frequent, consistent monitoring of SCr levels and reducing overall nephrotoxic burden not only shortens the durations of AKI episodes in neonates but also reduces the frequency of them occurring in general.[16, 17]

A strong body of literature has emerged to show that AKI episodes are not "one and done" events. In the past, it was thought that patients who experienced an AKI could recover with no long-term effects and with complete return of kidney function. Recent research, however, has shown that this may not be the case. Evidence has suggested that neonatal AKI accelerates maturation of the kidneys, decreases glomerular counts, and hinders any potential post-natal glomerulogenesis that may occur after birth in preterm neonates.[18] Inflammation from

AKI also triggers an immune response, where inflammatory cells flood the kidneys and further aggravate kidney injury.[19] This can collectively cause further injury to the kidneys and accelerate the infant's kidneys to chronic kidney disease (CKD) in childhood if no actions are taken to identify and mitigate the damage. The criteria for defining CKD has evolved over time, but a reduction in kidney function leading to a glomerular filtration rate of less than 60 $mL/min/1.72m^2$ is the widely accepted standard.[20, 21] A decline all the way to 15 $mL/min/1.72m^2$ indicates end stage kidney disease, which can only be treated with renal replacement therapy, such as dialysis or kidney transplantation.[22] CKD can manifest itself symptomatically in multiple ways, including hypertension and proteinuria, which can be indicative of structural kidney damage.[19, 23] While CKD is a chronic medical condition that has to be managed for a lifetime, diet or therapies including antihypertensives and renin-angiotensin system antagonists can help to decrease the severity of CKD, slow progression of kidney disease, and alleviate these symptoms.[23]

Neonatal AKI has effects that extend outside of the urinary system and adversely affect outcomes in other organ systems. While there are several connections that could be described here, the focus of this capstone project will be on the interactions between the kidneys and the respiratory system, specifically the lungs. This phenomenon is termed kidney-lung crosstalk. Under normal circumstances, the kidneys and lungs are tightly connected and work in tandem; renal vascular tone is modulated through balancing carbon dioxide, and oxygen is managed to enable the kidneys to concentrate urine.[24, 25] The lungs and kidneys work together to maintain a healthy acid-base balance in the body.[25] The inflammatory response mentioned previously which exacerbates kidney injury also is detrimental to the lungs, inhibiting their function as well.[16] The

systems work so closely together and experience similar outcomes through the sharing of similar cell compositions and hormonal pathways.[25]

Interestingly, through kidney-lung crosstalk, kidney injury can lead to lung injury, and vice versa, because of the structural similarities that the two organs share. Phenotypically, kidney-lung crosstalk manifests itself in several ways. Infants who receive extracorporeal membrane oxygenation (ECMO) as a result of cardiac or respiratory failure, for example, are significantly more susceptible to experience an AKI, with rates observed as high as 50% to 60% in some studies.[26] Conversely, fluid overload and kidney injury have also presented as risk factors for the need for long-term invasive ventilation.[27]

One of the primary respiratory outcomes associated with neonatal AKI is bronchopulmonary dysplasia (BPD), the most common chronic lung disease associated with prematurity.[28] BPD usually is the result of infection or trauma from invasive ventilation inflicted on premature infants' underdeveloped lungs.[29] Infants with BPD are almost one and a half times more likely to experience an AKI episode during a NICU admission.[28] Preterm infants with BPD that experience an AKI are significantly more likely to require oxygen during their hospitalization and are more likely to die during their admission than infants without an AKI.[29] Odds of moderate or severe BPD increase by almost four times for preterm infants who have experienced an AKI.[28] The effects of kidney-lung crosstalk have clearly been established; however, further research into the relationships between neonatal AKI and BPD, specifically how BPD predicts short- and long-term kidney outcomes, is needed to gain a better understanding of this relationship.

Significance

Neonatal AKI is a common outcome of prematurity and is associated with both short-term morbidities and chronic health outcomes. As previously mentioned, however, a standard AKI definition had not been widely accepted until the KDIGO guidelines for AKI were published in 2012, and a level of misunderstanding may still exist among some physicians regarding what constitutes an AKI. Single-center cohort studies have shown that a lack of clinical guidelines about the criteria for an AKI results in more frequent AKI episodes for infants admitted to the NICU, under-recognition of AKI on discharge paperwork, and reduction in long-term clinical monitoring with a nephrologist.[15, 30] One of these studies found that the implementation of standardized clinical practice changes such as nephrology rounds in the NICU dropped AKI episodes from 30% to 15%.[30]

Evidence has shown that preterm birth, AKI, and CKD are all closely linked to each other. Understanding the factors contributing to CKD progression is essential for informing the diagnosis of CKD early on as well as effective management of kidney health. When evaluating the factors leading to a CKD diagnosis, one must consider the whole body, not just the kidneys, in order to obtain a holistic picture of the patient and all potential variables contributing to the progression towards CKD. BPD commonly results from prematurity, and research strongly suggests its occurrence increases the odds of an AKI episode in premature infants. Thus, gaining a fuller understanding of how BPD affects kidney health is essential in gaining a full picture of a patient's risk for CKD.

Preliminary Data

The present study examines AKI incidence and CKD frequency in a sample of children from the Riley Hospital for Children BPD Database. Our study team conducted a pilot study using a portion of the database in the summer of 2021 to gather preliminary data on patient demographic and birth information, NICU outcomes, and long-term outcomes.[31] In this preliminary study, infants (n=265) were born at a median gestational age of 27 weeks with a median birth weight of 890 grams. Median APGAR scores were 4 and 7 at one and five minutes, respectively. Approximately half (53%) of infants experienced an AKI episode during their NICU admission, with only 30% of these AKI episodes being noted on discharge documentation. A significant number (77%) of infants had persistent renal dysfunction defined as a serum creatinine level over 0.5 mg/dL at two weeks of life. Our study team also found that after discharge, only 50% of infants monitored serum creatinine levels, 30.4% of infants had a urinalysis done, and 82.2% of infants had any recorded blood pressure measurements. For individuals with laboratory data post-NICU admission, 132 infants had elevated serum creatinine levels, forty-three had CKD (defined as a glomerular filtration rate of less than 90 $mL/min/1.72m^2$), eight had proteinuria, and thirty were hypertensive (a blood pressure over the ninety-fifth percentile for age and sex).

CHAPTER III

PROBLEM AND HYPOTHESIS

Neonatal AKI and BPD are two common outcomes associated with preterm birth. While it is known that the kidney and respiratory systems are tightly connected and that injury of one can often exacerbate or lead to injury of the other, few studies have examined the long-term effects of BPD, a chronic lung disease, in relation to AKI occurrence, progression to CKD, and overall kidney health. The present study examines both short- and long-term kidney outcomes in a population of infants with BPD, with the goal of better understanding the relationship between BPD and long-term kidney health. This study also explores the potential variables that may play a part in this relationship.

Hypothesis and Specific Aims

For this capstone project, I hypothesize that infants diagnosed with BPD will be more likely to experience CKD in childhood compared to infants that were not diagnosed with BPD. I predict that these infants with BPD also have a higher frequency of AKI episodes in early infancy, specifically during their NICU admission. The first objective of this study is to describe the incidence of AKI, a short-term outcome, among infants with BPD. The second objective of this project is to describe the incidence of CKD, a long-term outcome, among infants with BPD.

I will also examine other long-term outcomes, namely hypertension and proteinuria, among this same group.

Hypothesis: Infants with BPD will be more likely to experience CKD in childhood compared to other infants.

Specific Aim 1: Determine the incidence of AKI episodes in infants with BPD during their NICU admission.

Specific Aim 2: Determine the frequency of CKD and other long-term kidney outcomes (e.g., hypertension, proteinuria) in infants with BPD.

CHAPTER IV

RESEARCH METHODS

The Riley Children's Hospital BPD Database includes 1,058 individuals who received care at the Riley Hospital for Children NICU between 2010 and 2020. The database is an ongoing collaborative research and clinical care database which has been developed and maintained by neonatology and pulmonary physicians and researchers at Riley Children's Hospital. Patients were identified in Cerner using NeoData software[32] and were subsequently included in the database if they were alive at twenty-eight days and if their chart described a diagnosis of BPD during their NICU admission.[33] For this secondary study on patients previously identified and enrolled in the BPD database, additional data for each patient were retrospectively collected to describe demographic and birth information, kidney outcomes in the NICU, and kidney outcomes after discharge from the NICU. Pertinent medical data were collected by our research team and managed using REDCap electronic data capture tools hosted at Indiana University.[34] This study was approved by the Indiana University Institutional Review Board.

Demographic information included patient sex, date of birth, gestational age in weeks, birth weight, APGAR scores at one and five minutes, if the infant was small for gestational age, mode of delivery (vaginal or C-section birth), and if the infant was part of a multiple gestation pregnancy.

Kidney-specific outcomes in the NICU included AKI occurrence; type of dialysis, if needed; serum creatinine levels for the first week of hospitalization, at two weeks of life, and at discharge; cystatin C level at discharge; any nephrology consult; if AKI was coded on hospital documentation; diagnosis of neonatal hypertension; and date of discharge. An AKI occurrence was indicated if the patient's SCr either rose at least 0.3 mg/dL or increased by one and a half times the reference SCr value, or the previous lowest SCr value. If the patient was diagnosed with neonatal hypertension, any medications started for hypertension were recorded.

Kidney-specific outcomes after NICU discharge included established outpatient follow-up visits to nephrology and/or urology; any serum creatinine levels, urinalysis results, blood pressure readings, BUN levels, and cystatin C levels taken after discharge; any diagnosis of CKD and date of diagnosis; any diagnosis of proteinuria and age at onset; and any diagnosis of hypertension and date of onset. A CKD diagnosis was indicated if the patient had a glomerular filtration rate of less than 90 mL/min/1.72m^2. Proteinuria was defined as any presence of protein in the urine determined through urinalysis. Patients were determined to have hypertension after discharge if they had blood pressure readings over the ninety-fifth percentile for their age and sex.

For statistical analysis, categorical variables were compared with Pearson's chi-squared tests. Continuous variables were compared using Kruskal-Wallis tests. Categorical variables were summarized with frequencies and percentages, while continuous variables were summarized with median and interquartile ranges. Demographic and birth information, criteria for AKI definition, short-term outcomes of NICU admission, and long-term outcomes were analyzed using infants' AKI status during the NICU admission. Demographic and birth

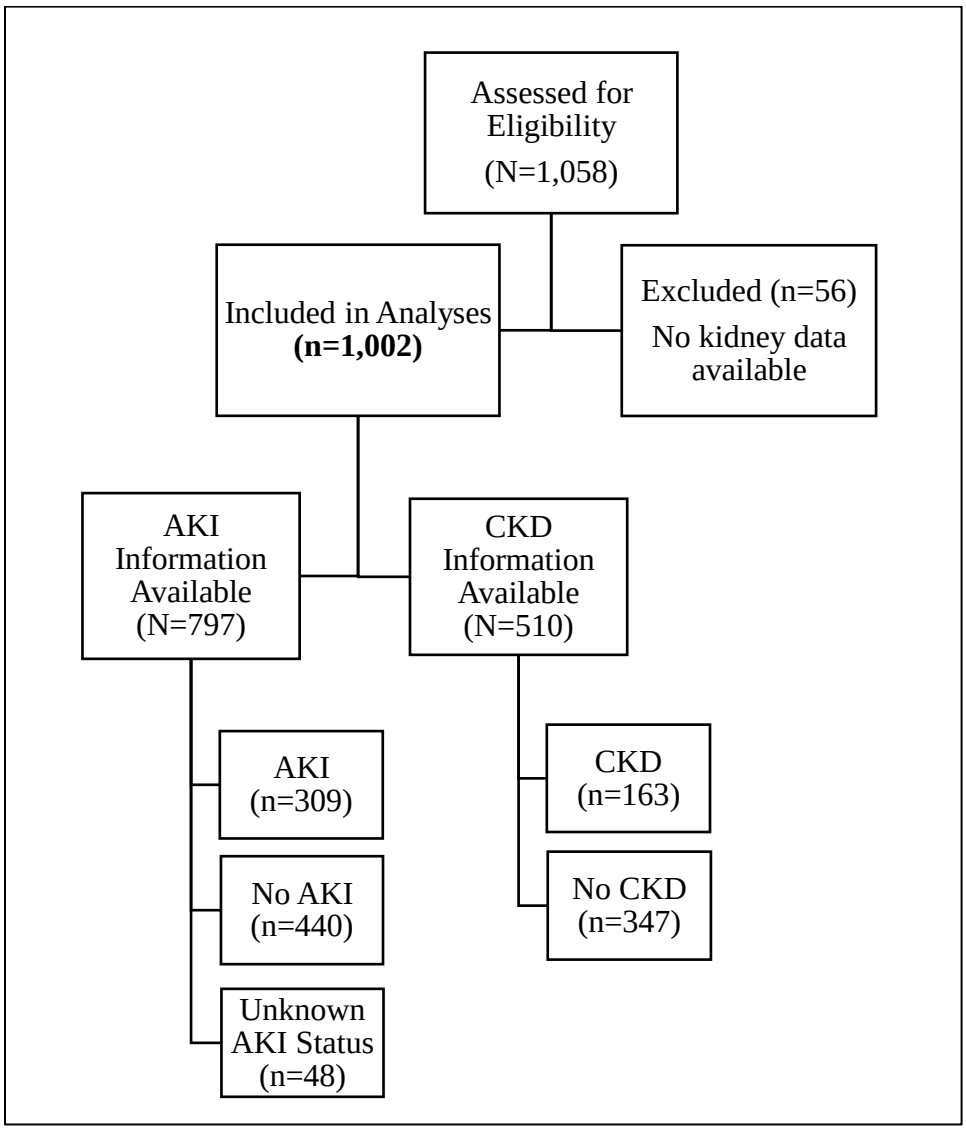
information and long-term renal outcomes were also interpreted with respect to childhood CKD diagnosis. Statistical analyses were conducted in the summer of 2022 using Stata/SE 17.[35]

CHAPTER V

RESULTS AND DISCUSSION

In this retrospective study, the medical records of children from the Riley Children's Hospital BPD Database were analyzed to better understand how AKI and BPD in the NICU potentially contribute to a future CKD diagnosis. AKI and BPD are common outcomes of prematurity. Studies have suggested that AKI and BPD are interconnected through kidney-lung crosstalk, and one or both of their occurrences could predict future onset of CKD. This study describes AKI frequency and CKD onset in a cohort of children with BPD, shedding light on specific areas where increased medical care and monitoring could minimize risk of progression to CKD and optimize long-term renal health.

FIGURE 1. CONSORT Flow Diagram



AKI, acute kidney injury; CKD, chronic kidney disease

One thousand fifty-eight patients were included in the initial BPD cohort. Of the 1,058, 56 were excluded from analyses due to not having any kidney available. One thousand and two patients were included in analyses of kidney outcomes. Of the 1,002 individuals, 797 had data about AKI status during their NICU course as well as complete demographic and birth information. Five hundred and ten of the 1,002 patients had data allowing us to evaluate CKD

status after discharge from the NICU. See FIGURE 1 for the CONSORT flow diagram describing patients that were included and excluded.

TABLE 2. Patient Demographic and Birth Characteristics Stratified by Acute Kidney Injury Status

Infant Characteristics	**Cohort N=797**	**AKI N=309**	**No AKI N=440**	**p-value[1]**
Gender				0.56
Male (n, %)	420 (52.7)	168 (54.4)	225 (51.1)	
Female (n, %)	377 (47.3)	141 (45.6)	215 (48.9)	
Gestational Age (n, %)				0.23
22-24 weeks	164 (20.6)	70 (22.7)	88 (20.0)	
25-27 weeks	392 (49.2)	137 (44.3)	231 (52.5)	
28-30 weeks	214 (26.9)	94 (30.4)	105 (23.9)	
≥30 weeks	27 (3.4)	8 (2.5)	16 (3.6)	
Small for Gestational Age (n, %)	83 (10.4)	30 (9.7)	47 (10.7)	0.69
Mode of Delivery (n, %)				0.023
Vaginal	211 (26.4)	94 (30.4)	104 (23.6)	
C-Section	507 (63.6)	195 (63.1)	287 (65.2)	
Unknown	70 (8.8)	20 (6.5)	49 (11.1)	
Multiple Gestation (n, %)	133 (16.7)	56 (18.1)	68 (15.5)	0.86
Birth Weight, grams (median, [IQR])	980 [665, 1210]	900 [726, 1158]	870 [704, 1127.5]	0.40
APGAR Scores (median [IQR])				
1 minute	4 [1, 6]	4 [2, 6]	4 [1, 6]	0.61
5 minutes	6 [5, 8]	7 [5, 8]	6 [4, 8]	0.16

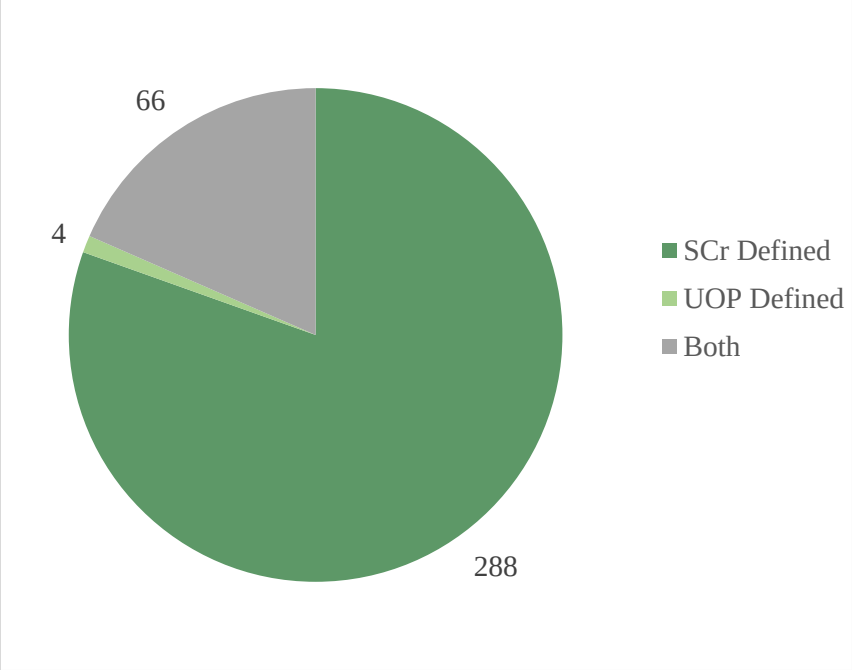
AKI, acute kidney injury; IQR, interquartile range

[1] p value compares those with AKI to those without AKI

Of those with known neonatal AKI status ("Cohort"), 52.7% were male and 47.3% were female. The mean gestational age was 26.4 weeks (SD=2.2), and the mean birth weight was 951.0 grams (SD=355.3). See TABLE 2 for a comprehensive list of demographic and birth characteristics stratified by AKI status.

An AKI episode occurred in 309 of 797 (38.8%) infants in the cohort. Forty-eight infants did not have enough information collected during their NICU admission documentation to determine if an AKI occurred and were marked as "Unknown" in data collection.

FIGURE 2. Frequency of Acute Kidney Injury Characterized by Serum Creatinine and/or Urine Output



For infants with AKI, the majority of cases (80.4%) were defined exclusively using SCr criteria (FIGURE 2). Only four patients (1.1%) experienced an AKI episode that was defined using UOP. A handful of patients (18.4%) had an AKI that was determined using both SCr and UOP.

TABLE 3. NICU Outcomes by Acute Kidney Injury Status

	AKI N=309	**No AKI N=440**	**p-value**
Persistently elevated SCr (n, %)	276 (89.3)	279 (63.4)	<0.001
Nephrology consulted during admission (n, %)	116 (37.5)	63 (14.3)	<0.001
AKI coded on discharge documentation (n, %)	156 (50.5)	-	-
Hypertension (n, %)	36 (11.7)	59 (13.4)	0.86

AKI, acute kidney injury; SCr, serum creatinine

Short-term NICU outcomes were recorded for each infant if the information was available (TABLE 3). Most infants experienced persistently elevated SCr levels at two weeks of life, regardless of if they experienced an AKI episode during their NICU admission. Patients with an AKI experienced significantly higher rates of persistently elevated SCr (89.3% vs. 63.4%, $p<0.001$) and nephrology consults during the NICU admission (37.5% vs. 14.3%, $p<0.001$) compared to infants who did not have an AKI episode. Of note, only one patient in the whole cohort required dialysis.

TABLE 4. Long-Term Renal Outcomes in Infants with Bronchopulmonary Dysplasia

	Frequency	**Percentage**
Outpatient Follow-Up Characteristics (N=1,002)		
Outpatient Nephrology Care	120	12.1
Outpatient Urology Care	180	18.1
SCr Evaluation after Discharge	525	52.4
Urinalysis Evaluation after Discharge	316	31.5
Blood Pressure Evaluation after Discharge	772	77.4
Kidney-Related Diagnoses After Discharge		
CKD after Discharge	163/510	31.7
Age at CKD Onset (median [IQR])	2.2 [1.6-3.9]	
Proteinuria after Discharge	41/328	12.5
Age at Proteinuria Onset (median [IQR])	4.7 [0.7-14.9]	
Hypertension after Discharge	114/752	15.2
Age at Hypertension Onset (median [IQR])	2.0 [1.1-4.1]	

SCr, serum creatinine; CKD, chronic kidney disease; IQR, interquartile range

Long-term renal outcomes were described for all infants included in analyses from the BPD database (N=1,002; TABLE 4). Half of patients had some SCr monitoring (52.4%), around one third had a urinalysis performed (31.6%), and a majority had blood pressure measurements (77.4%). Based off available laboratory data, CKD status was able to be determined in 510 patients of the entire cohort. CKD was diagnosed in 32.0% of these patients and at a median age of 2.2 years. Proteinuria was diagnosed in 12.5% of individuals at a mean age of 4.7 years. Hypertension onset occurred in 15.16% of patients at a mean age of 2.0 years.

TABLE 5. Patient Demographic and Birth Information by Chronic Kidney Disease Status

Infant Characteristics	**CKD n=163**	**No CKD n=347**	**p-value[1]**
Gender			0.26
Male (n, %)	69 (42.3)	151 (43.5)	
Female (n, %)	94 (57.7)	196 (56.5)	
Gestational Age (n, %)			0.36
22-24 weeks	35 (21.5)	75 (21.6)	
25-27 weeks	67 (41.1)	166 (47.8)	
28-30 weeks	50 (30.7)	87 (25.1)	
≥30 weeks	11 (6.7)	19 (54.8)	
Small for Gestational Age (n, %)	24 (14.7)	27 (7.8)	0.015
Mode of Delivery (n, %)			0.62
Vaginal	44 (27.0)	106 (30.5)	
C-Section	92 (56.4)	192 (55.3)	
Unknown	27 (16.6)	49 (14.1)	
Multiple Gestation (n, %)	39 (23.9)	52 (15.3)	0.014
Birth Weight, grams (median [IQR])	900 [710, 1160]	890 [685, 1125]	0.67
APGAR Scores (median [IQR])			
1 minute	5 [2, 6]	4 [2, 6]	0.60
5 minutes	7 [5, 8]	7 [5, 8]	0.61

CKD, chronic kidney disease; IQR, interquartile range
[1] p value compares those with CKD to those without CKD

Lastly, patient demographic and birth information was described for children with available long-term laboratory data describing CKD status (TABLE 5). One hundred sixty-three children (16.3%) experienced an observable progression to CKD of the whole cohort. Compared to patients without CKD, patients with CKD were smaller for gestational age (14.7% vs. 7.8%; p=0.015) and more likely to be part of a multiple gestation pregnancy (23.9% vs. 15.3%; p=0.014).

The results of this study show high frequencies of both short- and long-term kidney outcomes after NICU admission in a cohort of infants with BPD. Over a third of patients in the

cohort experienced an AKI. This rate is comparable to the AKI frequencies of critically ill infants found in the literature. A study by Askenazi et al. observed that of 923 critically ill infants receiving intensive care, 38.0% experienced at least one AKI of stage 1 or higher.[11] A separate multisite, multinational study similarly found that 29.9% of neonates experienced an AKI during their NICU hospitalization.[36] While low birth weight and low gestational age are two perinatal variables frequently cited as risk factors for neonatal AKI, this association was not observed in this cohort. Infants born at 25-27 weeks' gestation were the most common between both AKI and non-AKI groups, though this finding was not statistically significant.

It was also observed in this study that patients with an AKI had higher occurrences of both persistently elevated SCr and nephrology consults during their NICU admission compared to their non-AKI peers. Persistently elevated SCr in this case could be indicative of renal damage caused by antibiotics or drugs, alteration in perfusion to the kidneys caused by ventilatory requirements, or a reflection of other comorbidities associated with preterm birth. This finding is also consistent with the literature that AKI is not an isolated event but inflicts lasting damage on the kidneys, reflected in the elevation of SCr.[21]

Nearly 38% of those with an AKI had a nephrology consultation during their NICU admission. While this frequency is higher than some studies have suggested,[30, 37] this still means 62% of infants who experienced an AKI did not receive specialized renal care during their NICU admission. A 2022 study by Starr et al. found that uniform protocols for neonatal AKI identification significantly improved not only rates of nephrology consultation inpatient and follow-up in an outpatient setting, but also significantly decreased rates of AKI occurrence by up to 21%.[30] This finding emphasizes the importance of accurately identifying, treating, and monitoring AKI, especially in this population of critically ill infants.

We identified 163 children (16.3%) who progressed to CKD in this study. This is not far from other studies that have evaluated the frequency of CKD in children who had formerly received neonatal intensive care.[20, 38] Studies have found that CKD can be potentiated by AKI occurrence, repeated AKI episodes, and other factors such as low birth weight. These factors each affect the physiology of the kidneys in different ways, from reducing nephron and glomerular mass to accelerating renal maturation.[21] Patients in this study were more likely to develop CKD if they were small for gestational age or part of a multiple gestation pregnancy, where infants' ability to develop to term in utero can be affected. Interestingly, gestational age did not have a significant impact on future CKD progression in this cohort, though the incidence of CKD was higher among children born at a lower gestational age. This finding could suggest that other factors hold greater weight in determining if a child will develop CKD. Lastly, we observed that a portion of children in the cohort had proteinuria and hypertension (12.5% and 15.2%, respectively). Both proteinuria and hypertension can be indicative of impeded kidney function, suggesting a portion of the children in this group may be at risk of long-term kidney damage as a result of neonatal AKI or other renal damage.

CHAPTER VI

SUMMARY AND CONCLUSIONS

In conclusion, this study investigated the short- and long-term renal outcomes in a cohort of children with BPD. We observed that the children in this cohort had high frequencies of AKI and CKD, suggesting that BPD could increase the likelihood of experiencing an AKI episode during the NICU course or developing CKD in the future. Children who were small for gestational age or were a part of a multiple gestation pregnancy were more likely to progress to CKD, suggesting infants meeting these criteria may need additional monitoring for short- and long-term renal outcomes. Lastly, attention must be placed on the proper identification and monitoring of AKI in preterm neonates in order to minimize long-term renal damage as much as possible.

Limitations

I acknowledge there are several limitations to this study. First, there are not many studies that examine the relationship between AKI and BPD as well as any potential connections between BPD and CKD. This lack of literature added an extra challenge when understanding the foundations of this research question, but it presents an exciting opportunity to investigate a novel research question and to begin filling a gap in the current literature. Secondly, as this is a retrospective chart review study of individuals who were patients from 2010 to 2020 at Riley

Hospital for Children, there are several patients who were lost to follow-up over time and had various datapoints missing, limiting the dataset, the amount of longitudinal data that could be collected for these patients, and potentially underestimating chronic renal outcomes in this cohort. Most missing datapoints during the NICU admission were due to missing SCr values which therefore prevented us from knowing if the patient experienced a neonatal AKI. Missing datapoints after NICU discharge occurred primarily because some patients were transferred to different healthcare facilities for outpatient care, did not have outpatient visits, or additional hospitalizations and therefore did not have any additional laboratory values. Some of these missing datapoints also occurred due to patient expiration during the NICU admission. Lastly, AKI can be described by both changes in SCr levels and UOP, and the definitions may still differ among physicians. This may have caused different patients to have an AKI coded on discharge documentation over the course of the registry.

Future Directions

This project lays preliminary groundwork for exciting, innovative future research exploring the relationships between AKI, BPD, and CKD. More research in this area is needed to fully understand how the combination of AKI and BPD potentially lead to a CKD diagnosis in the future. The primary studies exploring this research question were retrospective, resulting in unavailable data and smaller cohort sizes. Longitudinal prospective studies following patients over the course of their nephrological care would therefore be beneficial, as data would be actively collected and trends in renal health could be followed in real time. Future studies should continue to evaluate methods for inpatient neonatal AKI identification and outpatient follow-up. Researchers have started investigating this important question in recent years, and more attention

to this area is warranted. Next steps for this could be developing systems for AKI identification and follow-up and testing these systems in various settings (i.e., NICU, pediatric ICU) for feasibility.

CHAPTER VII

CAPSTONE PROJECT EXPERIENCE

Project Site

This capstone project was conducted through my place of employment, Indiana University School of Medicine. I currently am a Clinical Research Specialist for Dr. Michelle Starr's lab in the Department of Pediatrics, Division of Nephrology. Our lab is also a part of the Pediatric and Adolescent Comparative Effectiveness Research (PACER) program, which is housed in the Department of Pediatrics to promote research in the department as well as to develop more efficient methods to implement in the healthcare system at large.

Journal Summary

I have worked at the Indiana University School of Medicine since March 2021. My daily responsibilities include patient recruitment from inpatient and outpatient healthcare facilities, screening NICU patients weekly for AKI to be followed by our renal team, assisting in manuscript preparation and submission, and coordinating with Indiana University's IRB to submit, amend, and audit studies. For the semester I worked on my capstone project, I dedicated most of my work hours to developing my capstone proposal and collecting data which contributed to this report. My journal describes what activities I did in relation to my work but also my capstone project.

APPENDIX

APPENDIX A

IRB APPROVALS

PROTOCOLS

INDIANA UNIVERSITY

APPROVAL LETTER

To: Cristea, A. Ioana

Protocol #: 1710518896

Protocol Title: Predictive Factors of Later Respiratory Outcomes

Type of Submission: Amendment

Level of Review: Expedited

Approval Date: Thursday, June 24th 2021

Expiration Date: no date provided

**If Expiration Date = "No date provided," this research does not require annual renewal; thus there is no expiration date.*

IRB-04 approved the above-referenced submission. Conduct of this study is subject to the IU HRPP Policies, as applicable.

Additional Notes:

Amendment A013
This research is approved under the following expedited category:
- Category 5

Documents approved with this submission:

Attachments

Protocol 1710518896 - Cristea - A008 - Protocol_final.docx A008 - Protocol

You should retain a copy of this letter and all associated approved study documents in your research records.

If you have any questions or require further information, please contact the HRPP via email at irb@iu.edu or via phone at (317) 274-8289.

3500 Camp Bowie Blvd
Fort Worth, TX 76107
NorthTexRegIRB@unthsc.edu
(817) 735-0409

DATE:	November 11, 2021
TO:	Stephen Mathew, Ph.D.
FROM:	North Texas Regional Institutional Review Board
PROJECT TITLE:	[1822474-1] Predictive Factors of Later Respiratory Outcomes
REFERENCE #:	2021-117
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	November 11, 2021
REVIEW CATEGORY:	Expedited review category # *5*

Thank you for your submission of New Project materials for this project. The North Texas Regional Institutional Review Board has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a project design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on applicable federal regulations {45 CFR 46.110 (b) (2)], per the following category:

(5) - Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)

The following items have been approved with your submission:

-Protocol synopsis

Additional IRB Comments:

• *NTR IRB accepts Indiana University IRB's Expedited approval of this study (approved on June 24th, 2021) which involves UNTHSC affiliates.*

• *Advise the IRB when UNTHSC involvement ends in this project by completing a Final/CloseOut Form*

You may ONLY use documents that have been IRB-approved and display IRB approval verification (print-stamping).

Please note that any revision to previously approved materials must be approved by the IRB prior to initiation. Please use the appropriate revision procedures for this activity.

Based on the Revised Common Rule (2018 Requirements), no annual review of this project is required. However, please seek review and approval of ANY changes, even if minor, made to the protocol prior to implementation. Additionally, please notify the IRB when the study has been completed.

All UNANTICIPATED PROBLEMS involving risks to subjects or others (UPIRSOs) and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office. Please use the appropriate reporting forms for this procedure. All FDA and sponsor reporting requirements should also be followed.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office within 10 business days of identifying the issue / complaint.

In addition, the Principal Investigator must notify the IRB immediately if any new potential Conflict of Interest arises.

Any research / key personnel involved in the study are also responsible for maintaining appropriate human subject protection educational training current.

SPECIAL FINDINGS:

- HIPAA Waiver: The Board finds this study meets all legal requirements for a Waiver of Individual Authorization under HIPAA pursuant to 45 CFR 164.512 (i) (2) (i)-(v) and approves the request.
- Informed Consent Waiver: The Board finds this project qualifies for a Waiver of Informed Consent (or alteration of some element of consent) under the provisions of 45 CFR 46. 116 (f)(3) (i)-(v).

If you have any questions, please contact Jessica Bird at 817-735-2081 or jessica.bird@unthsc.edu. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within North Texas Regional Institutional Review Board's records.

APPENDIX B

CAPSTONE PROJECT JOURNAL

Week 1: August 23, 2021 – August 27, 2021

- Worked on data entry for the BPD database.by pulling medical information from Cerner and inputting it into our REDCap database.
- Attended research training for new research coordinators at IU. Learned how to complete lab requisitions in Cerner.
- Went to North campus for outpatient nephrology clinic to recruit patients for a longitudinal neonatal AKI follow-up study.
- Worked on data entry for a project examining CRRT and ammonia levels.
- Attended a Zoom professional development course about Cerner tips and tricks.

Week 2: August 30, 2021 – September 3, 2021

- Worked on data entry for the BPD database.
- Worked on data entry for the CRRT/ammonia project.
- Attended weekly meeting with Michelle to discuss a recent study audit I did – my first internal audit.
- Worked on capstone proposal and presentation.

Week 3: September 6, 2021 – September 10, 2021

- Mostly out of town on vacation.
- Had capstone meeting with committee members. Received helpful feedback and learned more about what to expect for my defense in the future.

Week 4: September 13, 2021 – September 17, 2021

- Attended a professional development seminar for clinical research coordinators about adverse events and serious adverse events.
- Worked on data entry for the BPD database.
- Worked on data entry for the CRRT/ammonia project.
- Submitted not-for-cause audit for the neonatal AKI follow-up study to the IU IRB.
- Made recruiting calls for a focus group about physician communication of AKI/CKD in the NICU setting.

Week 5: September 20, 2021 – September 24, 2021

- Worked on data entry for the BPD database.
- Worked on data entry for the CRRT/ammonia project.
- Had site initiation visit with Watermark IRB today for a multi-site study examining outcomes of the Aquadex dialysis machine.

Week 6: September 27, 2021 – October 1, 2021

- Worked on data entry for the BPD database.
- Worked on data entry for the CRRT/ammonia project.

- Finished working draft of my capstone proposal document and forwarded it to committee members for review.
- Attended clinical research staff education (level 2) over the course of the week, where we learned about research ethics, financial awards process for clinical trials, HIPAA privacy and security procedures, and audit expectations and tips.

Week 7: October 4, 2021 – October 8, 2021

- Worked on data entry for the BPD database.
- Completed data entry for the CRRT/ammonia project.
- Attended outpatient nephrology clinic and recruited two families for the AKI follow-up study. I also recruited one of these families for the physician communication focus group.
- Went to the NICU and obtained informed consent and HIPAA authorization from a family to participate in the AKI follow-up study. Dropped off urine sample collection supplies with the nurse for them to collect a urine sample.

Week 8: October 11, 2021 – October 15, 2021

- Worked on data entry for the BPD database.
- Went to outpatient nephrology clinic at the North campus to recruit for the AKI follow-up study and physician communication study. Updated the REDCap database for the follow-up study with newest patients.
- Made phone calls to recruit for the AKI follow-up study and physician communication study.

Week 9: October 18, 2021 – October 22, 2021

- Worked on data entry for the BPD database.
- Stopped by the NICU to consent families for the AKI follow-up study and to drop off urine sample collection supplies with the appropriate nurses.
- Went to outpatient nephrology clinic and recruited several families for the AKI follow-up study.

Week 10: October 25, 2021 – October 29, 2021

- Worked on data entry for the BPD database.
- Updated the REDCap database for the AKI follow-up study. Reviewed patients' charts to make sure all laboratory values and outpatient visits were in the REDCap database.

Week 11: November 1, 2021 – November 5, 2021

- Worked on data entry for the BPD database.
- Went to outpatient nephrology clinic to recruit patients for the AKI follow-up study.

Week 12: November 8, 2021 – November 12, 2021

- Worked on data entry for the BPD database.
- Prepared a manuscript for submission to a journal by editing formatting and content based on the journal's guidelines for submission.

Week 13: November 15, 2021 – November 19, 2021

- Worked on data entry for the BPD database. Passed patient #900, meaning the finish line is in sight.
- UNTHSC IRB approved my capstone project.
- Went to outpatient nephrology clinic and recruited one patient for the physician communication focus group.

Week 14: November 22, 2021 – November 26, 2021

- Out of office: Thanksgiving week

Week 15: November 29, 2021 – December 3, 2021

- Worked on data entry for the BPD database.
- Helped the Research Jam team facilitate the physician communication focus group. A very educational, exciting experience getting a look into qualitative data analysis and focus group structure.
- Set up Oncore software for the Aquadex study in preparation for retrospective recruitment of patients who received dialysis with this device.

Week 16: December 6, 2021 – December 10, 2021

- Worked on data entry for the BPD database.
- Attended qualitative analysis sessions with the Research Jam team, which was a fantastic experience. Collected notes based on the focus group and grouped notes by themes/commonalities. This will be used to make a prototype of educational materials that

the nephrology team will hand out in the NICU for patients whose children experience an AKI.

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