ACUTE KIDNEY INJURY: IT'S NOT JUST ACUTE, AND IT'S NOT JUST THE KIDNEYS

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ACUTE KIDNEY INJURY: IT'S NOT JUST ACUTE, AND IT'S NOT JUST THE KIDNEYS

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EDITORIAL
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Editorial: Acute Kidney Injury: It's Not Just Acute, and It's Not Just the Kidneys

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Editorial on the Research Topic

Acute Kidney Injury: It's Not Just Acute, and It's Not Just the Kidneys

Acute kidney injury (AKI) occurs in ∼20, 30, and 40–60% of pediatric patients in pediatric, neonatal and cardiac intensive care units, respectively (1, 2). Twenty years ago, AKI in hospitalized children was considered an unfortunate consequence of illness, but ultimately self-limited without direct impacts on patient outcomes. Extensive research in the last 15 years revealed that AKI in hospitalized children is associated with greater hospital resource utilization, morbidity and hospital mortality (1, 3). Shockingly, many episodes of pediatric hospital-acquired AKI continue to go unrecognized (4). More recently, emerging evidence suggests that children surviving hospitalization with an AKI episode may be at substantially higher risk than children without AKI, for developing long-term chronic kidney disease (CKD) and hypertension and long-term mortality (5). This literature has contributed to a paradigm shift that AKI increases risk for poor long-term outcomes, warranting efforts to improve detection, management and secondary prevention of permanent sequelae.

The goals of this collection of 9 manuscripts are to provide an update on best practices for detection, management, and follow-up of pediatric AKI, and perspectives on the deleterious short- and long-term systemic sequelae of AKI in the context of evolving clinical, epidemiologic and fundamental AKI research.

In Impact of Acute Kidney Injury on Critically Ill Children and Neonates, authors Leghrouz and Kaddourah provide an overview of the recent shifts in AKI definition, now centering on the KDIGO defined criteria using either a rise in serum creatinine, and/or a reduction in urine output. The authors highlight the importance of measuring urine output in order to recognize oliguric AKI for improved diagnostic precision. The review also provides a summary of the impact of AKI following hematopoietic stem cell transplant and emerging data on children with multisystem inflammatory syndrome as a result of the SARS-CoV-2 pandemic.

In Acute Kidney Injury in Critically Ill Children Is not all Acute: Lessons Over the Last 5 Years, Hessey et al. reviewed the last 5 years of peer-reviewed literature exploring the long-term outcomes of pediatric AKI. The summary provides an overview of the advancements and remaining challenges in investigating long-term outcomes after critical illness in hospitalized children. It also highlights the importance of implementing standardized follow-up of kidney health and outcomes after an episode of severe AKI. This aligns with recent recommendations in the neonatal and pediatric response to the Acute Disease Quality Initiative (ADQI) 22 guidance document (6).

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In A Precision Medicine Approach to Biomarker Utilization in Pediatric Sepsis-Associated Acute Kidney Injury, authors Odum et al. reframe sepsis-associated AKI as a heterogeneous disease process. They provide a framework approach to utilizing biomarkers for prognostic enrichment and precision medicine to decluster the sepsis phenotype into distinctive pathophysiologies for targeted therapeutic clinical trials. This manuscript highlights the need to improve our understanding of AKI phentoypes for which future therapeutic targets might be considered.

In Continuous Renal Replacement Therapy in Critically Ill Children in the Pediatric Intensive Care Unit: A Retrospective Analysis of Real-Life Prescriptions, Complications, and Outcomes, Buccione et al. present new data from a 6-year single center retrospective study evaluating outcomes after CRRT therapy in pediatrics. Their data reports that fluid overload was the predominant indication for CRRT initiation (>60% of cases) and identifies catheter size <8 French and lack of citrate regional anticoagulation as predictors of early discontinuation of treatment. With a mean follow-up time of 3.5 years, only 42% of the patients who survived did not have any long-term kidney sequelae, including CKD or proteinuria.

In Two to Tango: Kidney-Lung Interaction in Acute Kidney Injury and Acute Respiratory Distress Syndrome, Alge et al. provide a thorough review of the basic science and clinical data surrounding the development of AKI-mediated lung injury and the role that lung injury plays in affecting kidney function. The review highlights the complexity of identifying the bidirectional effects of hemodynamic alterations in critical illness, resulting from acute lung disease as well as from AKI.

In A review on the application and limitations of administrative health care data for the study of acute kidney injury epidemiology and outcomes in children, Ulrich et al. summarize the opportunities and limitations of leveraging "big data" in administrative health repositories to investigate pediatric AKI outcomes. While big data research offers unique and unprecendented opportunities to evaluate pediatric AKI with large sample sizes, there is a need to validate these data for defining pediatric kidney outcomes and limiting associated biases.

In For Whom the Bell Tolls: Acute Kidney Injury and Electronic Alerts for the Pediatric Nephrologist, authors Nguyen and Menon review best practices for AKI alerts, and how they can be implemented to hasten the diagnosis and optimize management in pediatric AKI. These AKI alerts and tools tie in with broader efforts within the nephrology community to utilize artificial intelligence and machine learning to improve outcomes in patients with AKI. The review provides examples of early applications of alert tools in pediatric AKI, including a nephrotoxic-mediated AKI stewardship program, which has been shown to reduce the rate, severity and duration of nephrotoxic AKI (7, 8).

In Acute kidney injury in pediatric diabetic kidney disease, Piani et al. describe the pathophyisiology of AKI and its relation to diabetic kidney disease in children with types I and II diabetes mellitus. Children with diabetes are at an increased risk for developing AKI, and after an episode of AKI, they are at higher risk of developing diabetic kidney disease and CKD. The review also summarizes the increased risk of severe COVID-19 disease in patients with diabetes mellitus.

In Acute Kidney Injury and Pediatric Bone Health, authors Hegde et al. review the current literature on fracture risk after AKI, the mechanisms of dysregulation in bone metabolism in AKI, and suggest areas for future research, particularly with regard to skeletal growth in pediatric patients after AKI.

As the overall survival of critically ill pediatric patients improves, there are increasing survivors of childhood AKI. With these perspectives in mind, future research is required to explore the long-term impact of pediatric AKI on population health, health care costs, and how pediatric providers within varying healthcare contexts, can potentially improve care delivery with a goal to optimize their patients' outcomes later in life.

AUTHOR CONTRIBUTIONS

DS, AD, KG, and MZ contributed to the editorial writing and revision process. All authors contributed to the article and approved the submitted version.

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REVIEW
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Acute Kidney Injury and Pediatric Bone Health

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Acute kidney injury (AKI) has been associated with deleterious impacts on a variety of body systems. While AKI is often accompanied by dysregulation of mineral metabolism—including alterations in calcium, phosphate, vitamin D, parathyroid hormone, fibroblast growth factor 23, and klotho—its direct effects on the skeletal system of children and adolescents remain largely unexplored. In this review, the pathophysiology of dysregulated mineral metabolism in AKI and its potential effects on skeletal health are discussed, including data associating AKI with fracture risk.

Keywords: AKI, skeleton, parathyroid hormone, fibroblast growth factor 23, klotho, vitamin D, mineral, inflammation

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INTRODUCTION

Acute kidney injury (AKI) results from a spectrum of insults that lead to a sudden decrease in kidney function and is responsible for significant morbidity and mortality (1–3). The worldwide incidence of pediatric AKI in hospital settings ranges from 26.9 to 41.3% (2, 4). Associated mortality ranges from 8.8 to 21% and is inversely related to gross national income per capita (2, 4, 5). AKI is accompanied by systemic inflammation (6) and has been associated with distant-organ injury—including injury to the lungs (7–9), heart (10), intestines (11), liver (11, 12), and brain (13)—that contributes to short- and long-term adverse patient outcomes (14, 15). AKI is frequently accompanied by dysregulated mineral metabolism (16), supporting the hypothesis that AKI may also be accompanied by alterations in skeletal structure and function. Commonly encountered dysregulation in mineral metabolism during AKI includes hypocalcemia, hyperphosphatemia, elevated parathyroid hormone (PTH), decreased 1,25-dihydroxyvitamin D (1,25D), elevated fibroblast growth factor 23 (FGF23), and decreased klotho. These patterns are similar to those seen in individuals with chronic kidney disease–mineral bone disorder (CKD-MBD), a condition known to alter skeletal and vascular biology. Compared to CKD-MBD, much less is known about the effects of mineral dysregulation and inflammation in AKI on short- and long-term skeletal health (16–18).

Identifying independent risk factors for skeletal injury in AKI is challenging for a number of reasons. First, AKI is a heterogeneous diagnosis with a myriad of inciting and exacerbating factors. Second, short-term biomarkers of skeletal injury are lacking, and the timeframe over which skeletal outcomes occur is long. Nonetheless, in this review, we aim to summarize the existing literature in three areas: (1) current data on fracture risk following AKI; (2) potential mechanisms of dysregulation in AKI, including inflammation, which could impact skeletal health; and (3) areas for further research.

FRACTURE RISK AND AKI

There is a striking paucity of literature exploring the association between AKI and risk of skeletal fracture. A single population-based matched cohort study conducted among 448 Taiwanese adult patients who survived dialysis-requiring AKI and 1,792 controls demonstrated a 1.25-fold increased risk of bone fracture ($p = 0.049$) in the AKI recovery group, even after controlling for progression to end-stage renal disease (19). Enrollees were identified through national database entries over 8 years and were prospectively followed for at least 1 year after hospital discharge. Incidence of bone fracture was 320 per 10,000 person-years in the AKI recovery group and 93 per 10,000 person-years in the control group (19). Patients with skeletal fracture also experienced increased long-term mortality (hazard ratio = 1.43, 95% confidence interval = 1.19–1.71, $p < 0.001$) (19). This is the only study to date that has evaluated long-term impacts of AKI on risk of skeletal fracture. Individuals with non–dialysis-dependent AKI and individuals younger than 18 years were not included in the study. These findings should be replicated in broader cohorts of adults with milder degrees of AKI and in children, as mineral dysregulation after AKI has been demonstrated in both groups (16, 20). There is also little published literature describing histologic changes in bone during or following AKI, with only one report describing findings from bone biopsy, including mild increases in bone resorption without increased osteoid (21).

MINERAL DYSREGULATION AND AKI

Hypocalcemia and Hyperphosphatemia

The majority of total body calcium and phosphate is stored as skeletal hydroxyapatite, with extracellular calcium representing ∼1% and extracellular phosphate representing <1% of total body stores (22, 23). Extracellular calcium and phosphate concentrations are primarily regulated by three hormones: 1,25D, PTH, and FGF23 [**Figure 1**; (24)]. Dysregulation of calcium and phosphate homeostasis is a consistent finding in studies of adult patients with varying severities of AKI (25–33). In a study of 400 critically ill adults with AKI, patients had a median phosphate level of 5.2 mg/dL with an interquartile range of 4.0–6.7 mg/dL (29). Additionally, multiple studies comparing mineral metabolism in patients with AKI to hospitalized control groups without AKI demonstrated significantly higher phosphate levels in AKI groups (28, 30, 31, 33). For example, in a cohort of 51 children who underwent elective cardiac surgery, serum phosphate increased significantly over a 24-h period in those who developed AKI compared to those who did not ($p = 0.01$) (34).

Of the aforementioned case-control studies that reported significantly elevated phosphate levels, two measured serum calcium levels. Leaf et al. reported significantly lower calcium levels in 30 adult patients with all-cause AKI compared to 30 patients without AKI ($p = 0.004$) (30). Patients with AKI had a serum calcium interquartile range of 7.5–8.6 mg/dL, and patients without AKI had an interquartile range of 8.1–9.0 mg/dL (30). In contrast, Zhang et al. did not detect a statistically significant difference in ionized calcium levels between critically ill adult patients with and without AKI ($p = 0.41$) (28). Patients with and without AKI had mean ionized calcium levels of 1.19 ± 0.1 mmol/L and 1.15 ± 0.08, respectively. Both studies are limited by small sample size, although differing findings could be explained by heterogeneous study populations (all hospitalized patients vs. only critically ill patients) and methods of measuring calcium (total serum vs. ionized). Hypocalcemia would be expected to follow significant hyperphosphatemia as elevated serum phosphate sequesters calcium. However, patients who are critically ill are also more likely to have aberrations in albumin and acid–base balance (22), causing a potential change in ionized calcium but not in total serum calcium. In addition to affecting ionized calcium levels, metabolic acidosis *in vitro* has been demonstrated to directly trigger osteoblast inhibition and osteoclast stimulation in mouse models (35).

Hypocalcemia and hyperphosphatemia may have acute as well as subacute clinical relevance (22). Acute hypocalcemia has well-described effects on decreasing peripheral vascular resistance (36), decreasing myocardial contractility (37), and increasing neuromuscular reactivity (22). Further research is needed to better understand the clinical impact that mineral alterations in AKI have on skeletal health, particularly among children undergoing rapid skeletal growth.

MECHANISMS OF MINERAL DYSREGULATION IN AKI

1,25 Vitamin D

Alteration in regulatory hormones contributes to calcium and phosphate derangements following AKI. Decreased levels of 1,25D, and less frequently its precursor 25-hydroxyvitamin D (25D), have been described in multiple adult AKI cohorts, including in patients status post-cardiac surgery (26), those with rhabdomyolysis (27), and those with critical illness (29). There is growing evidence in adults that a history of critical illness is itself a strong risk factor for osteopenia and osteoporosis likely due to a combination of inflammation, undernutrition, immobilization, and vitamin D deficiency (38)—all of which are compounded by AKI. Similarly, vitamin D deficiency is common in critically ill children, with a pooled prevalence of 54.6% in a recent systematic review of hospitalized children with acute or critical conditions (39). Vitamin D deficiency, especially in critically ill patients, is linked to increased risk of AKI and mortality (40, 41). This link underscores the salience of investigating how vitamin D dysregulation during AKI superimposed on frequently reported baseline vitamin D deficiency may be contributing to adverse outcomes, including adverse skeletal outcomes.

Studies comparing 1,25D and 25D levels in adults with AKI to hospitalized controls without AKI have demonstrated significantly lower levels of 1,25D but not 25D (31, 42, 43). However, Tingting et al. reported lower levels of both 1,25D ($p < 0.0001$) and 25D ($p < 0.0001$) among 34 patients with critical illness and AKI compared to 12 healthy controls (44). Demographic differences in gender, age, and race between groups did not rise to statistical significance (44). This study's findings are perhaps explained by their use of healthy controls, as studies utilizing hospitalized controls have not shown differences in

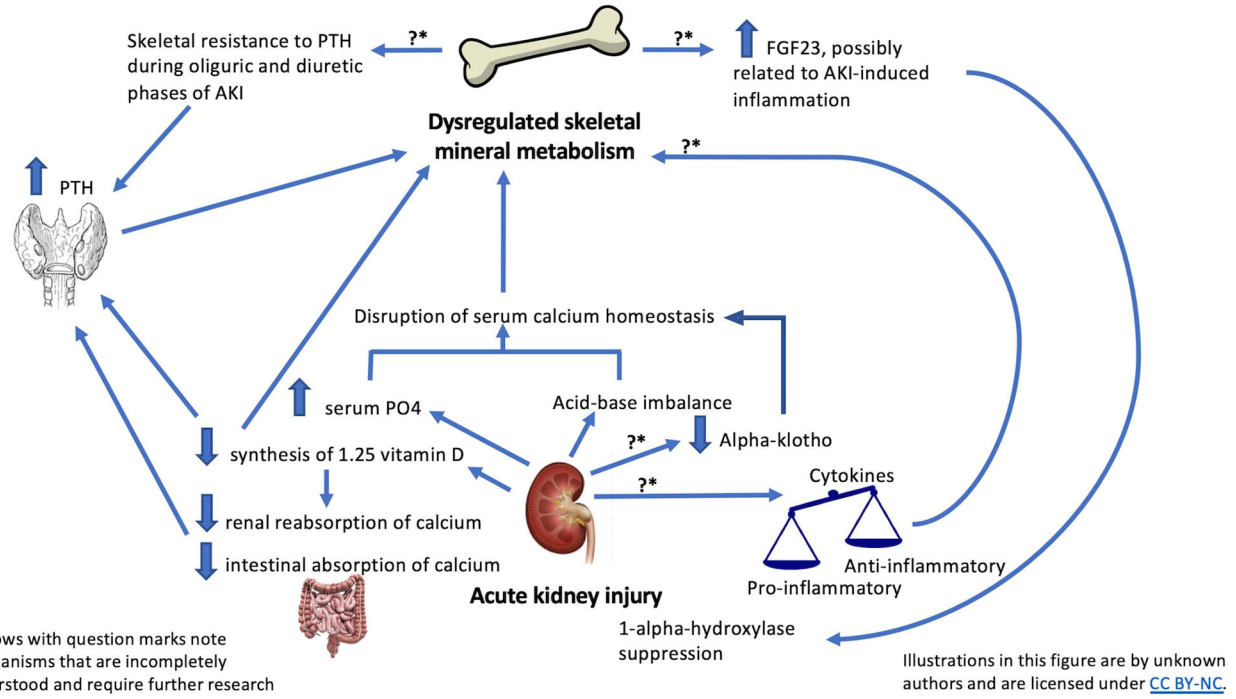

FIGURE 1 | Summary of possible mechanisms linking AKI and skeletal outcomes.

25D, suggesting that low 25D may be a marker of global disease severity more so than of acute mineral dysregulation. Comparatively, Lai et al. enrolled 200 patients with AKI, 13 critically ill patients without AKI, and 17 healthy participants and reported that 1,25D levels but not 25D levels were significantly lower in the AKI group vs. the other groups (42). Taken together, these data suggest that AKI is associated with suppression of 1,25D and variable changes in 25D (16).

1,25D deficiency contributes to decreased intestinal absorption of calcium and decreased renal reabsorption of calcium (24, 45). These changes in AKI are thought to be mediated by decreased renal synthesis of 1,25D secondary to proximal tubule injury or from FGF23-induced suppression of 1-α-hydroxylase (46). Substrate delivery of 25D to the proximal tubule in AKI may also decrease because of lower levels of circulating vitamin D–binding protein (DBP), decreased filtration of 25D-DBP complexes due to reduced glomerular filtration rate (GFR), and decreased uptake of these complexes for processing due to proximal tubule injury (16).

Altered vitamin D metabolism in AKI, in addition to vitamin D deficiency potentially present on admission or attributed to critical illness, may be clinically relevant in multiple ways. Vitamin D plays a key role in skeletal health, mitigating fracture risk, and optimizing bone density and content through direct mineral regulation (47). 1,25D, through binding to its nuclear receptor, may also play a role in immune and inflammatory regulation (48). Even though vitamin D deficiency in AKI is likely transient, resolving with renal recovery (26, 27, 49), it has been associated with endothelial dysfunction (50), oxidative stress, and inflammation—both in the renal microvasculature and in distant organs (14, 51, 52). Arfian et al. demonstrated renoprotective effects of vitamin D—including reducing myofibroblasts and renal inflammation—in mice with kidney ischemia–reperfusion injuries (IRIs), although protective effects of vitamin D on distant organs such as bone following AKI have not yet been elucidated (52).

Parathyroid Hormone

PTH is the primary regulator of serum calcium, and elevated PTH levels have been frequently reported in patients with AKI (16, 17, 26, 27, 29). Studies have consistently demonstrated significantly elevated PTH in individuals with AKI compared to healthy controls (44, 53, 54). These elevations are thought to be secondary to hypocalcemia and low serum 1,25D levels as discussed above (24). Upregulation of the parathyroid calcium-sensing receptor due to acute inflammation may additionally affect the calcium-PTH set-point (16, 24).

Skeletal and renal resistance to PTH has been described in humans following AKI (25, 29, 30), potentially contributing to dysregulated hormonal control of calcium and phosphate. In patients with CKD, skeletal resistance to PTH is thought to be secondary to downregulated PTH receptors (16); however, specific mechanisms of PTH resistance in AKI have not been studied. Massry et al. demonstrated that patients with AKI failed to respond appropriately to exogenous PTH infusion during their oliguric and diuretic phases of AKI but produced appropriate increases in serum calcium once renal function recovered (25).

Thus, skeletal resistance to PTH in AKI is likely a transient phenomenon, as is elevated PTH (26, 30). For example, in a study comparing PTH levels in hospitalized adults with and without all-cause AKI, PTH levels were initially higher in the AKI group ($p = 0.004$) compared to the non-AKI group but were no longer different by day 5 of enrollment ($p = 0.56$) (30). Additional studies of hospitalized adults with and without AKI following cardiac surgery and critical illness (28, 31) have reported that PTH was comparatively elevated (and occasionally severely, with PTH >250 mg/dL) in AKI groups but did not rise to statistical significance. Small sample sizes and heterogeneous patient populations may explain these inconsistent findings. Likewise, findings may be confounded by elevations of PTH due to critical illness (55, 56).

Fibroblast Growth Factor 23 and Klotho

FGF23 is a bone-derived protein, produced by osteoblasts and osteocytes and known to regulate vitamin D metabolism and phosphate homeostasis (57–59). FGF23 was first identified in patients with tumor-induced osteomalacia and mineralization defects and has since become an important link connecting renal and skeletal physiology (60). Studies have consistently demonstrated that FGF23 levels increase rapidly after onset of AKI (28–31, 61–66). In mouse models of folic acid–induced AKI, FGF23 levels have been shown to rise within 1 h following AKI (62). In adults with AKI after cardiac surgery, FGF23 levels demonstrated more than a 15-fold increase at 24 h post-surgery (62).

While there is strong evidence of a role for FGF23 in mediating phosphate and vitamin D dysregulation in early-stage CKD (67), the effects of FGF23 on skeletal health following AKI have not been studied (61, 68). Rise in FGF23 following AKI appears to be independent of PTH and 1,25D levels (20, 58, 62, 69), but resultant effects of FGF23 on PTH and 1,25D levels in AKI have yet to be conclusively demonstrated. FGF23 is also thought to play a role in the inflammatory response following AKI (58). In mice with folic acid–induced AKI, very high *FGF23* mRNA expression was detected in thymus and spleen, suggesting that FGF23 may be associated with increased *TNF* expression and elevated inflammatory cytokine levels through effects on lymphoid organs (58).

FGF23 elevation is likely altered in a timeframe consistent with reduced renal function. For example, in 32 pediatric patients who underwent cardiac surgery requiring cardiopulmonary bypass, those children who developed post-operative AKI demonstrated a significant increase in intact FGF23 at 2 h post-reperfusion compared to those who did not develop AKI ($p = 0.04$). At 48 h, intact FGF23 levels between these groups were not significantly different ($p = 0.19$), although C-terminal FGF23 levels were significantly elevated ($p = 0.006$) in the AKI group (20). Animal models of AKI due to folic acid nephropathy have demonstrated increased FGF23 expression in femur lysates, but the factors responsible for this elevation in bone during a period of acutely reduced renal function have not been identified (58, 62, 64).

α-Klotho, a transmembrane protein mainly produced by renal tubular epithelial cells, plays a critical role in FGF23 receptor binding (16) and, through its actions on the kidney and parathyroid glands, plays an important role in mineral metabolism (64, 70, 71). Its extracellular domain can modulate renal calcium and potassium absorption independently of FGF23 (16, 72) in the distal tubule and can be cleaved into the circulation, facilitating distant organ effects of FGF23 (64). In CKD mouse models, klotho has been shown to decrease ectopic calcification (including soft tissue calcification), likely through tight coregulation of phosphorous with FGF23 (70). Klotho deficiency has been demonstrated in animal models of AKI (73, 74), although studies in humans are lacking (64, 71, 73, 75–78). Cytokines produced during AKI, including tumor necrosis factor α (TNF-α), may downregulate renal expression of klotho (79). No studies have yet examined whether klotho deficiency may contribute to aberrant calcification in AKI.

Inflammation in AKI

Acute intrarenal and systemic inflammation, including the release of proinflammatory cytokines, has been well-described following AKI (6, 7, 11–14, 80–84). Inflammation is a crucial biologic response for eliminating pathogens and repairing injured tissue. However, the balance between proinflammatory and anti-inflammatory responses is often abnormal in AKI (83). In renal IRI, cellular damage triggers an inflammatory response that includes oxidative stress in renal tubular epithelial cells, necrotic cells that release a variety of molecules to signal damage, and cytokine release from activated renal parenchymal cells and dendritic cells that recruit innate and adaptive immune mediators (83).

Increased serum levels of proinflammatory cytokines, including TNF-α, interleukin 6 (IL-6), and IL-8, have been described during AKI in animal models of renal IRI (80). These animal models have demonstrated dramatic increases in plasma cytokine levels compared to non-IRI animal models, including sham surgery and bilateral nephrectomy (80). Similar increases in cytokine levels have been noted in trauma patients with AKI compared to those without AKI early on in their hospital courses (80). Circulating cytokines during AKI have been shown to impact distant organs, including the brain (13), liver (11), and lungs (8). In addition to increased cytokine production, experimental models indicate that cytokine clearance is also decreased in AKI (80).

Although direct effects of proinflammatory cytokines specifically on bone during AKI have not been studied, proinflammatory cytokines have been associated with adverse effects on bone formation and resorption [**Figure 1**; (85–87)] For example, TNF-α and IL-6 have been shown to activate the parathyroid calcium-sensing receptor (88) and to inhibit renal expression of 1-α-hydroxylase (89), which could contribute to hormonal dysregulation of mineral metabolism in AKI. TNF-α has been reported to inhibit *PHEX* gene expression. *PHEX* gene is expressed mostly in osteoblasts, and loss of PHEX function has been linked to defective mineralization (90). Additionally, data from the Women's Health Initiative Study (91) suggest that TNF-α plays a role in mediating fracture risk, as association between estimated GFR and fracture risk was eliminated after adjustment for TNF-α receptor levels.

Anti-inflammatory cytokines are also increased in AKI (83). IL-10 is an anti-inflammatory cytokine that may have osteoprotective effects and has emerged along with IL-6 as a key player in signaling distant effects of acute renal inflammation (81). IL-10 is produced by T-regulatory cells (60) that *in vitro* directly inhibit osteoclast activity, including their differentiation and function, and *in vivo* have been shown to protect against TNF-α-induced bone loss in mice (92). The net outcome of this interplay between osteotoxic and osteoprotective factors on bone in the setting of AKI has yet to be determined (83).

Transcriptomics research in a murine model of ischemic AKI identified increased levels of IL-10 and IL-6 in lung tissue after AKI, in addition to global transcriptomic changes and histologic injury (81). Similar to the lung, the skeletal system has an extensive capillary network, including in the metabolically active skeletal system of children and adolescents undergoing periods of rapid growth (93). Thus, the relationship of inflammation in AKI and its potential direct consequences on bone health is an area ripe for additional investigation (80, 84).

AREAS FOR FUTURE RESEARCH

1. Epidemiological studies are needed to further characterize the burden of and risk factors for skeletal complications, including fractures, in patients with AKI. These studies should include pediatric patients, who are experiencing AKI during times of bone mineral accrual and linear growth (24).
2. Larger studies are needed to better characterize which aspects of dysregulated mineral metabolism, if any, persist after renal recovery following AKI.
3. The use of bone imaging (dual energy x-ray absorptiometry / high resolution peripheral quantitative computed tomography) lends itself to investigations into whether changes in bone structure and microarchitecture are seen in the acute or subacute phases of AKI.
4. Further investigation is needed regarding the extent to which systemic vascular and inflammatory changes detected following AKI, including vitamin D–associated changes, alter bone epigenetics and transcriptomics and might contribute to effects on long-term skeletal health. Metabolomics studies in AKI may identify downstream targets relevant for additional investigation (10, 94).
5. Although the pathophysiology of AKI generally involves a common cascade of inflammation secondary to ischemia, reperfusion, cell injury, and cell death, AKI remains a clinically heterogeneous diagnosis with varying therapies. The potential compounding effect of frequently used therapies in AKI, such as diuretics and other medications (87), on mineral dysregulation and bone health has not been evaluated.

AUTHOR CONTRIBUTIONS

AH and DG contributed to the literature review and layout of this article. AH wrote the first draft of the manuscript, which was revised by DG. AH, DG, and MD contributed to final manuscript revision and have approved the submitted version. All authors contributed to the article and approved the submitted version.

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REVIEW
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Acute Kidney Injury in Critically Ill Children Is Not all Acute: Lessons Over the Last 5 Years

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Acute kidney injury (AKI) in the pediatric intensive care unit (PICU) is an important risk factor for increased morbidity and mortality during hospitalization. Over the past decade, accumulated data on children and young people indicates that acute episodes of kidney dysfunction can have lasting consequences on multiple organ systems and health outcomes. To date, there are no guidelines for follow-up of surviving children that may be at risk of long-term sequelae following AKI in the PICU. This narrative review aims to describe literature from the last 5 years on the risk of medium and long-term kidney and non-kidney outcomes after AKI in the PICU. More specifically, we will focus on outcomes in children and young people following AKI in the general PICU population and children undergoing cardiac surgery. These outcomes include mortality, hypertension, proteinuria, chronic kidney disease, and healthcare utilization. We also aim to highlight current gaps in knowledge in medium and long-term outcomes in this pediatric population. We suggest a framework for future research to develop evidence-based guidelines for follow-up of children surviving an episode of critical illness and AKI.

Keywords: acute kideny injury, chronic kidney disease, long-term follow up, hypertension, healthcare utilization, mortality, critical care

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INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt onset of kidney dysfunction. AKI occurs in 20–30% of the general pediatric intensive care (PICU) population and up to 50% in children following cardiac surgery (1–6). Compared to children who do not develop AKI in the PICU, children with AKI are at higher risk of poor early outcomes, including mortality, receipt and longer duration of mechanical ventilation, and prolonged length of PICU and subsequent hospital stay (7–10).

More recently, research has focused on evaluating the medium and long-term sequelae of AKI sustained in the PICU. One of the largest early follow-up studies found that 10% of children with AKI in the PICU developed chronic kidney disease (CKD) [defined as glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 or albuminuria] 1–3 years later (11). Additionally, 47% of children with AKI were considered to be at risk of CKD [defined as GFR 60–90 ml/min/1.73 m^2, hypertension, and/or hyperfiltration (GFR $\geq$ 150 ml/min/1.73m^2)]. In 2014, Greenberg et al. performed a

systematic review and meta-analysis to examine the long-term kidney outcomes after AKI (12). These early studies found that children with AKI had higher rates of hypertension, proteinuria, CKD, and mortality relative to the general pediatric population. However, the authors highlighted that there was significant heterogeneity between studies with an absence of contemporaneous patients with no AKI, and variable definitions of AKI, which together made it difficult to evaluate the association between AKI and outcomes. These issues have been addressed systematically in recent studies standardizing AKI definitions, with large study cohorts that include non-AKI comparison groups, and an overall increase in the quality of research and rigor of analyses. This has allowed for a better understanding of the association between AKI and long-term outcomes.

The objectives of this narrative review are to: (i) summarize literature over the past 5 years for relevant medium and long-term outcomes following AKI in the general PICU population and children undergoing cardiac surgery; (ii) highlight risk associations for reported adverse outcomes; and (iii) discuss future directions for clinical guidelines and research to mitigate adverse outcomes in this high-risk population.

MORTALITY

Previous studies evaluating short- and long-term mortality following AKI lacked non-AKI comparison groups, however, they uniformly highlight that mortality rates in patients with AKI were higher than in the general population (12, 13). Since 2015, we identified eight studies that examined the association of AKI with mortality and compared this to children who did not develop AKI, with follow-up ranging from 28-days to 5–7 years (**Table 1**) (3, 6, 14–19). As highlighted in **Table 1**, despite differences in study populations and duration of follow-up, all studies reported higher mortality in those with AKI when compared with children who did not experience AKI whilst in the PICU, independent of illness severity and other important confounders.

General PICU Population

In a multinational study of 4,984 general PICU patients, Kaddourah *et al.* showed that severe AKI [defined throughout this review as stage 2 or 3 AKI by Kidney Disease: Improving Global Outcomes (KDIGO) criteria unless specified] was associated with 77% greater odds of 28-day mortality following adjustments for risk factors that differed between survivors and non-survivors including admission diagnoses, comorbidities, illness severity, and PICU interventions (3). Similarly, when compared to those with no AKI, a large multicenter Canadian study observed that severe AKI was associated with over 5 times greater risk of mortality 1-year after PICU admission following adjustment for illness severity and other important confounders (6). It is important to highlight that both these studies included in-hospital mortality from initial admission in their outcomes. In the Canadian study 52 (5.5%) patients died, 18 of whom died after discharge. Severe AKI was still associated with post-discharge mortality [odds ratio [OR] (95% confidence interval [CI]): 2.84 (10.4–7.81)] (6).

The longest follow-up study looked at mortality 5–7 years after hospital discharge in a non-cardiac surgery PICU population and found that AKI was associated with over 3 times higher risk of mortality (17). Interestingly, this paper demonstrated that the association between AKI and 30-day and 1-year mortality was conditional on the inclusion of hospital mortality in the outcome. When hospital mortality was included, AKI was associated with 30-day and 1-year mortality with a similar magnitude of association as reported in previous studies (3, 6, 17).

Cardiac Surgery Population

Two studies specifically focused on mortality in children with AKI following cardiac surgery. In a multicenter study of over 400 patients, Nune et al. found that children with severe AKI post-cardiac surgery had over 11 times higher risk of mortality 30-day after surgery, following adjustment for age, surgical risk score, cardiopulmonary bypass time, and cyanotic heart disease (18). In a similar-sized population, Hirano et al. reported a higher risk of 2-year mortality in children with AKI [defined by Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) criteria] post-cardiac surgery [adjusted hazard ratio (95% CI): 7.47 (2.88–19.40)] (16). Both of these studies included hospital mortality from the initial cardiac surgery admission.

What's New?

Since the publication of the systematic review by Greenberg et al. we now have comparable groups (with and without AKI during hospitalization) that allow us to evaluate the association between AKI and mortality (12). All studies found that children who develop AKI in the PICU had higher mortality, independent of illness severity measures, compared to patients admitted to the PICU who did not develop AKI. However, it is important to highlight that many of these studies included in-hospital mortality from the index admission.

HYPERTENSION, PROTEINURIA, AND CHRONIC KIDNEY DISEASE

In adult studies, AKI in the ICU is independently associated with significantly worse long-term kidney outcomes including hypertension, proteinuria, and CKD (20–22). The potential mechanism for the progression of AKI to CKD includes loss of kidney mass during the acute event resulting in progressive hyperfiltration damage, glomerulosclerosis, and fibrosis (23). This relationship has been challenging to study in the pediatric population as a result of the known physiologic maturation in glomerular filtration rate following birth, the current lack of consensus guidelines on how best to monitor these children over time resulting in varying follow-up practices, and inconsistent definitions of long-term kidney outcomes in the literature. Initial findings showed a higher prevalence of adverse kidney outcomes following AKI compared to the general population; however, in these studies subject numbers were small, follow-up duration

TABLE 1 | Summary of studies evaluating the association between AKI and mortality published over the past 5-years.

References	Study design	*N* patients	Inclusion criteria	AKI definition	Duration of follow up	Outcome definition	Findings
Sanchez-Pinto et al. (14)	Single center retrospective cohort study	8,260	General PICU, non-cardiac surgery	KDIGO	28-days	Chart review, includes in-hospital mortality	• In adjusted analysis both resolved and persistent AKI was associated with 28-day mortality
Al-Otaibi et al. (15)	Single center retrospective cohort study	131	General PICU	pRIFLE	2-years	Chart review, includes in-hospital mortality	• 40% 2-year mortality in patients with AKI • In adjusted analysis stage 3 (failure) was not statistically significantly associated with 2-year mortality
Hirano et al. (16)	Single center retrospective cohort study	418	Cardiac surgery	pRIFLE	2-years	Prospective patient database, includes in-hospital mortality	• 23 of 104 (22%) patients with AKI died during 2-year follow-up • AKI was associated with 2-year mortality [aHR 7.47 (2.88–19.40)]
Kaddourah et al. (3)	Multinational, prospective observational cohort study	4,984	General PICU	KDIGO	28-days	Chart review, includes in-hospital mortality	• 60 of 543 patients (11%) with severe AKI died compared to 105 of 4,140 patients (2.5%) without severe AKI ($P < 0.001$) • Severe AKI associated with increased risk of death [aOR 1.77 (1.17–2.68)]
Hessey et al. (17)	Two center retrospective cohort study	2,041	General PICU, non-cardiac surgery	KDIGO	5–7 years	Administrative data, excludes in-hospital mortality	• AKI was associated with over 3× higher risk of 5–7 year mortality • AKI was not associated with 30-day or 1-year mortality when hospital mortality excluded
Alobaidi et al. (6)	Multicenter retrospective cohort study	1,017	General PICU	KDIGO	1-year	Administrative data, includes in-hospital mortality	• 56 (5.5%) of patients died within 1 year of PICU admission • Severe AKI associated with greater 1-year mortality [aOR 5.50 (2.76–10.96)] • Post-discharge mortality ($n = 18$) was higher in patients with severe AKI [aOR 2.84 (1.04–7.81)]
Nunes et al. (18)	Multicenter prospective cohort study	402	Cardiac surgery	KDIGO	1-year	Chart review, includes in-hospital mortality	• Severe AKI associated with increased risk of 30-day mortality [aHR 11.7 (1.9–72.6)] • At 1-year 4 of 344 (1.2%) non-AKI/stage 1 and 5 of 58 (8.6%) stage 2 or 3 AKI died
Zhang et al. (19)	Single center retrospective cohort study	80	Liver transplantation	KDIGO	3-year	Chart review, includes in-hospital mortality	• The 3-year survival was higher in non-AKI patients (95%) compared to AKI patients (87%) but did not reach statistical significance

Key articles evaluating the association between PICU-AKI and long-term mortality published since 2015. This may not be an exhaustive list as a formal systematic review search was not performed.

KDIGO, Kidney Disease: Improving Global Outcomes; pRIFLE, pediatric Risk, Injury, Failure, Loss, End stage renal disease; AKI, acute kidney injury; aOR, adjusted odds ratio; aHR, adjusted hazard ratio; PICU, pediatric intensive care unit; CKD, chronic kidney disease; SCr, serum creatinine.

was limited, and many lacked non-AKI comparison groups (12). Since 2015 we found eleven studies examining the association between PICU-AKI and hypertension, proteinuria, and CKD (**Table 2**) (2, 4, 15, 24–32).

General PICU Population

There have been four studies examining the association of CKD following AKI in general PICU cohorts. The follow-up time across these studies varied from 2 to 6 years, as did the methods

TABLE 2 | Summary of studies evaluating the association between AKI and long-term kidney outcomes published over the past 5-years.

References	Study design	*N* patients	Inclusion criteria	AKI definition	Duration of follow up	Outcome definition	Findings
Cooper et al. (24)	Single center retrospective cohort study	51	Cardiopulmonary bypass surgery	pRIFLE	7 years	(i) low eGFR (<90 ml/min/1.73 m^2) (ii) albuminuria (ACR >30 mg/g) (iii) Hypertension (≥90th percentile)	• No significant association between outcome measures of CKD and PICU-AKI after CPB surgery
Hollander et al. (2)	Single center retrospective cohort study	88	Heart transplant recipients	KDIGO	1 year	(i) eGFR<60 mL/min/1.73 m^2 for more than 3 months	• 5% of population developed CKD • Non-recovery from AKI associated with CKD
Al-Otaibi et al. (15)	Single center retrospective cohort study	131	General PICU	pRIFLE	2 years	(i) Hypertension (>95th percentile) (ii) Proteinuria (PCR > 30 mg/dl) (iii) Reduction in GFR	• PICU patients with AKI had high prevalence of CKD (33%) and hypertension (73%)
Madsen et al. (4)	Multicenter retrospective cohort study	382	Cardiac surgery	KDIGO	5 years	(i) low eGFR (<90 ml/min/1.73 m^2)	• AKI associated with an increased risk for CKD [aHR 3.8 (1.4–10.4)]
Greenberg et al. (25)	Single center prospective cohort study	110	Cardiopulmonary bypass surgery	AKIN	5 years	(i) low eGFR (<90 ml/min/1.73 m^2) (ii) albuminuria (ACR > 30 mg/g) (iii) Hypertension (≥95th percentile)	• No significant association between outcome measures of CKD and AKI
Hessey et al. (26)	Two center retrospective cohort study	2,235	General PICU	KDIGO	5 years	(i) ≥1 CKD diagnostic code or ≥1 CKD-specific medication prescription	• Patients with AKI had increased risk of a CKD diagnosis
Benisty et al. (27)	Two center prospective cohort study	277	General PICU, non-cardiac surgery	KDIGO	6 years	(i) low eGFR (<90 ml/min/1.73 m^2) (ii) albuminuria (ACR>30 mg/g) (iii) BP ≥90th percentile	• AKI and stage 2 or 3 AKI associated with 2.2- and 6.6-fold higher adjusted odds of CKD and pre-hypertension or worse
Hessey et al. (28)	Two center retrospective cohort study	1,978	General PICU, non-cardiac surgery	KDIGO	5 years	(i) ≥1 hypertension diagnostic code or ≥1 hypertension-specific medication prescription	• Patients with AKI and stage 2 or 3 AKI had increased risk of a hypertension diagnosis
Huynh et al. (29)	Two center retrospective cohort study	58	Neonatal cardiac surgery	KDIGO	6 years	(i) low eGFR (<90 ml/min/1.73 m^2) (ii) albuminuria (ACR>3 mg/mmol) (iii) BP ≥90th percentile	• Cardiac surgery associated AKI was not associated with CKD or hypertension
Menon et al. (30)	Single center retrospective cohort study	221	Heart transplant recipients (*n* = 109) Liver transplant recipients (*n* = 112)	KDIGO	5 year	(i) low eGFR (<60 ml/min/1.73 m^2)	• No difference in incidence of CKD amongst heart transplant recipients with PICU-AKI vs. no AKI • Liver transplant recipients with PICU-AKI showed a higher risk of CKD compared to those with no AKI
Zappitelli et al. (31)	Two center prospective cohort study	124	Cardiac surgery	KDIGO	4 years	(i) low eGFR for age (ii) albuminuria (ACR > 30 mg/g) (iii) Hypertension (≥95th percentile)	• AKI not associated with CKD and hypertension at follow-up

Key articles evaluating the association between PICU-AKI and long-term kidney outcomes including CKD, proteinuria, and hypertension published since 2015. This may not be an exhaustive list as a formal systematic review search was not performed.

KDIGO, Kidney Disease: Improving Global Outcomes; pRIFLE, pediatric Risk, Injury, Failure, Loss, End stage renal disease.; AKIN, acute kidney injury network criteria; AKI, acute kidney injury; aHR, adjusted hazard ratio; PICU, pediatric intensive care unit; CKD, chronic kidney disease; SCr, serum creatinine; eGFR, estimated glomerular; CPB, cardiopulmonary bypass.

of defining outcomes. However, consistently across all studies patients with mixed etiology, PICU-AKI were at higher risk of developing hypertension, proteinuria, and/or CKD over the long-term (15, 26–28). Two studies in cohorts of general PICU-AKI patients measured outcomes using laboratory defined CKD (albumin/creatinine >30 mg/g or GFR <90 ml/min/1.73 m^2) or measured office blood pressure abnormalities (15, 27). The prevalence of CKD and hypertension was high in the AKI population in both studies. One of these studies by Benisty et al. found that 6 years after PICU admission any AKI (i.e., stage 1, 2, or 3 by KDIGO criteria) and severe AKI (stage 2 or 3) were associated with a 2.2 [95% CI: 1.1–4.4] and 6.6 [95% CI: 1.5–28.3] higher adjusted odds ratio for CKD and pre-hypertension or worse, respectively (27).

Two studies from the same cohort in Quebec alternatively used administrative data (diagnostic and medication codes) to define CKD and hypertension outcomes (26, 28). In this large two-center retrospective cohort of 2,245 subjects, even following mild (stage 1) AKI, children had a significantly increased risk of CKD diagnosis after a 5-year follow-up period (26). At follow-up, 2% had a diagnosis of CKD. Those with mild AKI (stage 1) had an increased risk of CKD with an adjusted hazard ratio of 2.2 [95% CI:1.1–4.5]. Those with more severe AKI (stage 2 or 3) had a higher risk of CKD with an adjusted hazard ratio of 2.5 [95% CI: 1.1–5.7] (26). Looking exclusively at hypertension diagnosis based on administrative data in the same large two-center cohort, Hessey et al. found that patients with PICU-AKI had over twice the risk of a hypertension diagnosis with an adjusted hazard ratio of 2.19 [95% CI: 1.47–3.26] (28).

Cardiac Surgery Population

Six studies reported long-term kidney outcomes following PICU-AKI exclusively in subjects who underwent cardiac surgery (2, 4, 24, 25, 29, 31). Unlike the general PICU population, there is conflicting evidence on whether AKI after cardiac surgery is associated with negative long-term kidney outcomes. A two-center prospective cohort study of 124 children undergoing cardiac surgery found no association between AKI and CKD or hypertension after 2 years (31). The overall prevalence of CKD and hypertension was high at 20 and 30%, respectively, and young age at surgery was the only factor associated with CKD development. Contradicting these findings, in a single-center retrospective cohort study of 382 subjects who had undergone congenital cardiac surgery, after a median 3-year follow-up period, 11% of patients with AKI demonstrated CKD (4). The hazard ratio for CKD development amongst those with AKI compared with the non-AKI group was notably high, at 3.8 [95% CI: 1.4–10.4] following adjustment for sex, age, and surgical complexity (4). Similarly, two studies looking at long-term kidney outcomes exclusively in subjects who had undergone cardiopulmonary bypass surgery did not find an association between AKI and CKD (GFR <90 ml/min/1.73 m^2 or albuminuria) or hypertension (blood pressure >95th percentile) (24, 25).

In a cardiac sub-group of 88 heart transplant recipients, advanced CKD (GFR<60 mL/min/1.73 m^2) developed in 5% of the population after 1-year follow-up and was more common in those who did not fully recover kidney function and in those with more severe AKI (stage 2 or 3 by KDIGO) (2). Lastly, in an exclusively neonatal cohort of 58 subjects who underwent cardiac surgery, with a median follow-up of 6 years, AKI was not associated with CKD or hypertension despite a high prevalence overall (17 and 30%, respectively) (29). Post-operative cyanosis was the only independent predictor of CKD.

Biomarkers have been explored as a way to detect kidney injury earlier than rising serum creatinine and to predict hospital outcomes in both adult and pediatric settings (33–37). These biomarkers are also being explored as possible markers of CKD and its progression (38). Two pediatric studies looked at the long-term changes in biomarkers, both in cardiac surgery populations. The Translational Research Investigating Biomarker End Points in AKI (TRIBE-AKI) consortium found that urinary neutrophil gelatinase-associated lipocalin (NGAL) and urinary interleukin-18 (IL-18) concentrations rose acutely postoperatively in children with AKI but then decreased by the 5-year follow-up (25). They did not find a difference in median urine biomarker levels in children with severe AKI at 5-year follow-up compared to non-AKI patients. Unlike the TRIBE-AKI study, the Follow-Up Renal Assessment of Injury Long-Term After Acute Kidney Injury (FRAIL-AKI) study demonstrated that 7–8 years after cardiac surgery, children with AKI had higher urinary IL-18, kidney injury molecule-1 (KIM-1), and liver-type fatty acid-binding protein (L-FABP) concentrations (24). Despite these changes in biomarker profiles, these studies have not reported higher risk associations for adverse kidney outcomes in children with AKI post-cardiac surgery.

What Is New?

One of the major improvements in published studies since 2015 has been the standardization of AKI definitions, the inclusion of non-AKI comparison groups, and standardized definitions of hypertension, proteinuria, and CKD. The previous meta-analysis found an overall high prevalence of adverse kidney outcomes in AKI populations, however, more recent studies with non-AKI comparison groups and larger cohorts allow us to better understand this population's long-term risk (12). In the general PICU population, AKI is associated with an increased risk of CKD and hypertension compared to the non-AKI population after controlling for important confounders using both measured outcome data and administrative data. In the cardiac surgery population, intriguingly this risk association remains less clear, however as previously highlighted, this population has a high prevalence of kidney outcomes in long-term follow-up (12). Early research on the use of biomarkers for evaluating kidney recovery or CKD development has been published but validation of these biomarkers against gold standard measurements of kidney function are needed before they can be widely used.

HEALTHCARE UTILIZATION

In adults, AKI is associated with an increased risk of rehospitalization. In this population, the KDIGO guidelines suggest follow-up care 3 months after an AKI episode to assess new onset or worsening CKD (i.e., assess serum creatinine,

urine for protein, blood pressure) (39–41). Limited data have been published on the impact of AKI on long-term healthcare utilization in children following their initial admission to the PICU. Two studies reporting on healthcare utilization, one in a non-cardiac surgery population and the other in those following cardiac surgery, have been published (**Table 3**).

General PICU Population

In the non-cardiac surgery PICU population, although there was no association with increased emergency department visits in those who developed AKI, children with AKI had a 35% higher risk of 1-year hospitalization, and 59% higher risk of 5-year hospitalizations compared to children without AKI (5). AKI was also associated with increased physician visits over 5 years [relative risk (95% CI) 1.12 (1.07–1.18)]. Importantly, <25% of the children with AKI saw a nephrologist in a 5-year follow-up (5). The reason for nephrology follow-up was not reported nor was a diagnosis of CKD or hypertension, however, this still highlights that even children with severe AKI in the PICU do not have regular follow-up with kidney specialists.

Cardiac Surgery Population

In the cardiac surgery population, neither any AKI (i.e., stage 1, 2, or 3) nor severe AKI (stage 2 or 3 by KDIGO criteria) were associated with 30-day or 1-year hospital readmission (18). Unlike the aforementioned study in the non-cardiac population which evaluated the number of events per person-time (count data), this study focused on readmissions as a binary outcome. Therefore, further research evaluating cumulative use healthcare is required to better understand if there are differences in healthcare utilization in this population.

What's New?

Evaluating the impact of AKI on long-term healthcare utilization is a new area of research that has emerged in the pediatric literature over the past 5 years. At this time, it remains unclear if AKI itself contributes to increased healthcare utilization in the general PICU population either by long-term kidney and non-kidney sequelae that may progress following AKI or if perhaps, AKI is a marker of a patient's medical complexity. Due to the limited data on healthcare utilization following AKI in the PICU, we are not able to draw strong conclusions at this time. Research comparing healthcare utilization prior to critical illness and after critical illness (i.e., a difference-in-difference approach), specifically evaluating AKI as a risk factor, would help to clarify this. Although there are currently no guidelines for post-discharge monitoring after pediatric AKI, non-cardiac surgery children who experience AKI whilst in PICU may require closer follow-up by primary care providers, hence leading to increased physician visits. In those following cardiac surgery, this is "in built" to their current care pathways with sub-specialist cardiac reviews and follow-up. Research on provider practice is needed to further evaluate this.

DISCUSSION

With the development of a standardized definition for AKI and increased awareness of long-term sequelae of AKI described in the adult literature, more research evaluating pediatric AKI and long-term outcomes has been reported (21, 39). In the general PICU population, AKI is associated with an increased risk of long-term mortality, healthcare utilization, CKD, and hypertension. In the cardiac surgery population, the association between AKI and long-term outcomes is less clear; however, these children remain at high risk of kidney sequelae compared to

TABLE 3 | Summary of studies reporting AKI and long-term healthcare utilization published over the past 5-years.

References	Study design	*N* patients	Inclusion criteria	AKI definition	Duration of follow up	Outcome definition	Findings
Hessey et al. (5)	Two center retrospective cohort study	2,041	General PICU, non-cardiac surgery	KDIGO	5 years	30-day, 1-year, and 5-year hospitalizations, ED visits, and physician visits based on administrative data	• Patients with AKI (yes/no) and stage 2 or 3 AKI had increased risk of a 1- and 5-year hospitalization and 5-year physician visits • AKI was not associated with emergency department visit
Nunes et al. (18)	Multicenter prospective cohort study	402	Cardiac surgery	KDIGO	1-year	30-day and 1-year hospital readmission by chart review	• Patients with AKI did not have increased 30-day or 1-year readmission post-cardiac surgery compared to non-AKI patients • Stage 2 or 3 AKI was not associated with 30-day [aHR 1.5 (0.6–3.8)] or 1-year [aHR 0.98 (0.5–1.7)] readmission post-cardiac surgery

Key articles evaluating the association between PICU-AKI and healthcare utilization published since 2015. This may not be an exhaustive list as a formal systematic review search was not performed.

KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury; aHR, adjusted hazard ratio; PICU, pediatric intensive care unit; ED, emergency department.

the general population. Since the meta-analysis by Greenberg et al. published in 2014, non-AKI comparison cohorts have been included in research studies allowing for the evaluation of AKI with long-term outcomes rather than simply making comparisons with the general pediatric population (12). This has not only allowed us to identify AKI as an important risk factor for poor long-term outcomes, but it has also allowed us to quantify the magnitude of risk of developing these outcomes.

Over the past 5 years, more data has been published beyond early mortality (within 28-days) describing both medium (1–2 year) (6, 15, 16, 18) and long-term mortality risk (>3 years) (17, 19). Importantly, only two studies evaluated post-discharge mortality (i.e., excluded hospital mortality from the index admission). While the focus of this review was on long-term outcomes, we included key studies evaluating 28-day mortality as we felt this data frames the population and demonstrates the differences in risk of mortality during the acute illness and the long-term. This data highlights potential future research directions and the need to focus on evaluating in-hospital vs. post-discharge mortality to improve our understanding of the timelines and etiologies of mortality risk in this heterogeneous population of children with hospital-acquired AKI.

There remains a divergence of reported long-term kidney outcomes in children who developed PICU-AKI. Larger cohorts with general PICU populations show a consistent association between PICU-AKI and hypertension, proteinuria, and CKD. In exclusively cardiac surgery populations this association is less clear and requires further investigation. It remains to be shown if this is a result of study cohort size and shorter follow-up duration, if it is due to differences in the patient population, or the management of the patients in the peri-operative period or subsequently in the immediate post-operative period. It is well-known that there is a high prevalence of AKI after cardiac surgery and this is associated with poor short-term outcomes. There may be more strategies in place to identify and mitigate post-operative declines in kidney function. This population of patients needs further evaluation in larger multi-center cohorts with longer follow-up duration to better determine the long-term risk of kidney sequelae.

Biomarkers are an important emerging area of research and may allow for earlier detection of both acute and chronic kidney problems. However, standardized methods for measuring biomarkers and validated CKD definitions showing biomarker level associations with gold standard GFR measurements in children are needed before they can be widely used. At this time, proteinuria is the urinary marker used to identify early kidney disease. Disappointingly, rates of proteinuria are not reported uniformly in studies evaluating long-term CKD. However, this is important information as monitoring albumin-to-creatinine ratio or protein-to-creatinine ratio in a child with previous AKI is a simple investigation, less invasive than serial serum creatinine measurements, and may detect early kidney disease in this population.

All the studies that evaluated the long-term risk of kidney outcomes report composite measures, which include some combination of hypertension, proteinuria, albuminuria, and reduced GFR. Although composite measures have been used in the literature, moving forward it is important to report kidney outcomes more systematically, categorizing by presence (yes/no) and where applicable, by level for proteinuria, albuminuria, hypertension, CKD, and reduced eGFR. Detailed reporting is likely to improve our understanding of kidney outcomes, as often CKD is used as a "blanket term." Before these recent publications, there was little data on the prevalence of kidney outcomes in the pediatric AKI population, and these diagnoses are relatively uncommon in the general pediatric population. Therefore, early studies likely used composite measures to first assess if there was an association between AKI and long-term kidney outcomes. With the data showing increased prevalence of kidney outcomes in this population, future studies should aim to report these data with improved granularity using consensus definitions.

With many medical systems transitioning to electronic medical records, we are beginning to see larger population-based studies emerge in the pediatric AKI literature (6). While prospective follow-up studies provide exceptional information, these are labor-intensive and costly, and the retention of patients can be a challenge. Using administrative data is a cost-effective method for examining long-term outcomes in a large population. A systematic review in adults has demonstrated that AKI is identified by administrative health data with low sensitivity, but high specificity; similar results were also obtained from a validation study for identifying AKI in the PICU (42, 43). Adult studies have used databases to evaluate the association between AKI and long-term CKD development (22). In the pediatric literature, studies have started exploring the use of administrative data; however, the algorithms used to define CKD and hypertension have not yet been validated (26, 28). A validation study of long-term kidney outcome definitions with administrative data would allow for much larger population based studies with longer follow-up times. Validation studies in adults have demonstrated low sensitivity of these diagnostic code algorithms which is a major limitation (44, 45). These administrative data definitions seem to identify the more severe disease and therefore are likely to underestimate the prevalence of outcomes. It is important to identify the population of patients with early CKD or mild proteinuria, as early intervention can slow the progression of the disease. In the future, as more electronic medical record databases become available, combining what we have learned from administrative database studies with patient measurements will allow for larger population studies with more sensitive outcome measurements.

Recovery from AKI has also been an important variable to monitor in this population and has been associated with long-term CKD development in children (46). Unfortunately, in retrospective studies, this can be difficult to assess as many patients with AKI do not have repeat creatinine measurements (47). At this time there is no standardized definition for kidney function recovery and therefore studies evaluating AKI recovery with outcomes can be difficult to compare and interpret. Further research is needed to examine the association between incomplete recovery after AKI and long-term outcomes. Various definitions should be evaluated in these studies to better determine what level of incomplete recovery puts children at

higher risk. This information would be invaluable for long-term follow-up guideline development and risk stratification.

As our detection and treatment of various illnesses in the PICU improves, so does PICU survival; however, this may also be associated with greater long-term morbidity (48). At this time, it remains unclear whether the association between AKI and long-term mortality and healthcare utilization is related to the direct effect of kidney damage or if AKI is a marker of medical complexity. This also means further exploring the impact AKI has on long-term health-related quality of life (HRQoL). One study in children with sepsis in the PICU showed that children with severe AKI (stage 2 or 3 by KDIGO) had poorer HRQoL at 3-months than children with no AKI or stage 1 AKI (49). Future research is needed to further assess the relationship between AKI and long-term markers of morbidity. These studies should also evaluate other clinical factors that may contribute, to allow for more targeted risk stratification models and follow-up guidelines.

There are many important outcomes that have been explored in the adult AKI literature that remain as gaps in knowledge in the pediatric population. Specifically, there are validated administrative data definitions for kidney outcomes, more evidence on recovery after AKI as well as recurrent AKI events, and measures of quality of life (44, 45, 50, 51). Adult studies have also shown that AKI increases direct and indirect healthcare costs and resource utilization (50). These outcomes remain as gaps in our current pediatric AKI research and warrant further attention. The use of standardized AKI definitions and non-AKI comparison groups should also be continued in all future pediatric AKI research.

Overall, it is clear from the literature that children with PICU associated AKI have an increased risk of adverse medium and long-term outcomes including mortality. Future challenges include standardizing our approach to the recognition and management of these patients beyond the critical care and nephrology healthcare professionals. It is important therefore to have the diagnosis of AKI documented when the patient is discharged from the PICU and subsequently from the hospital so that both non-critical care professionals who are hospital-based and those outside the hospital know to monitor these children more closely for resolution of AKI and for long-term sequelae. This would also allow providers to make more educated decisions about future treatments, including avoiding nephrotoxic medications where possible and providing lifestyle modification advice. To date, outlines of possible follow-up guidelines have been suggested but no formal guidelines exist (52, 53). Adult AKI guidelines suggest assessing the resolution of AKI 3 months after the initial insult (39). As highlighted in this review, children who develop severe AKI in the PICU are at increased risk of adverse kidney and non-kidney outcomes, so similar follow-up recommendations are required.

The 22nd Acute Disease Quality Initiative (ADQI) conference recently published quality improvement recommendations for pediatric AKI (46). This consensus statement recommends kidney health assessment every 1–2 years, which includes an AKI history, blood pressure measurement, serum creatinine measurement, and drug list review, in high-risk populations which include patients admitted to the PICU. They also recommended kidney health assessment following an unplanned acute exposure such as PICU admission (46). These recommendations need evaluation for implementation in different health settings but are a welcome expert consensus statement that is likely to mitigate adverse outcomes in this high-risk population. One of the challenges of developing AKI guidelines in this population remains that all children with AKI cannot be followed by nephrologists alone both because of large numbers of patients (6) but also because of the increasing burden of healthcare visits on children and families. Therefore, a coordinated effort must be made between general pediatricians and practitioners that follow these children in the community and the discharging hospitalist or specialists. While future research will continue to help us better understand additional risk factors for long-term outcomes and develop better risk stratification models, it is clear that children with PICU-AKI require closer follow-up. Early CKD and hypertension are treatable and timely detection and intervention will improve outcomes in these children.

AUTHOR CONTRIBUTIONS

EH conceptualized the review, performed the literature review, and drafted and edited the manuscript. NM conceptualized the review, assisted with the literature review, drafted and edited the manuscript, and provided expert knowledge. MS conceptualized the review, assisted with the literature review, edited the manuscript, and provided expert knowledge. RA assisted with the literature review, edited the manuscript, and provided expert knowledge. EU, CM, and SB provided expert knowledge and edited the manuscript. All authors agreed to the final submitted manuscript.

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For Whom the Bell Tolls: Acute Kidney Injury and Electronic Alerts for the Pediatric Nephrologist

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With the advent of the electronic medical record, automated alerts have allowed for improved recognition of patients with acute kidney injury (AKI). Pediatric patients have the opportunity to benefit from such alerts, as those with a diagnosis of AKI are at risk of developing long-term consequences including reduced renal function and hypertension. Despite extensive studies on the implementation of electronic alerts, their overall impact on clinical outcomes have been unclear. Understanding the results of these studies have helped define best practices in developing electronic alerts with the aim of improving their impact on patient care. As electronic alerts for AKI are applied to pediatric patients, identifying their strengths and limitations will allow for continued improvement in its use and efficacy.

Keywords: acute kidney injury, electronic alerts, clinical decision support system, care bundles, electronic health record

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INTRODUCTION

Acute kidney injury (AKI) is commonly seen in hospitalized children, particularly those who are critically ill, and/or have underlying medical conditions (1, 2). It is independently associated with prolonged hospital stay and an increased risk of mortality (3). Post-hospital discharge, patients with AKI have higher healthcare utilization and are at risk of developing long-term consequences such as proteinuria, reduced renal function, and hypertension (4). Thus, the ability to detect these episodes of AKI can improve the management of these patients to provide the best care possible. However, AKI is often under-recognized and under-documented (5, 6). With the widespread use of electronic health records (EHR), it has become possible to use a variety of clinical decision support systems (CDSS) to improve patient care (7). These include automated alerts that allow providers to receive real-time notifications when triggered by a particular threshold. AKI is an ideal clinical condition for the use of electronic alerts because it has a consensus definition and it can be diagnosed from data available in EHR (8). In this review, we discuss the best practices for AKI alerts, special considerations when developing such tools for children, and its impact on patient outcomes.

BEST PRACTICES FOR AKI ALERTS

The 15th Acute Dialysis Quality Initiative (ADQI) consensus conference focused on utilizing EHR to predict AKI risk and outcomes (8–11). They recognized AKI alerts as an opportunity to prompt earlier evaluation and intervention, and provided guidelines around the development of electronic alert systems. One of the recommendations of the 15th ADQI conference was to further refine the structure of AKI alerts and to link them to actionable interventions for AKI care. More recently, the 22nd ADQI consensus conference provided quality improvement (QI) initiatives around the

identification and care of patients with AKI. They recognized the role of bundled interventions in preventing AKI or reducing the severity in patients at risk for AKI. The key recommendations from these consensus conferences are summarized here, highlighting particular challenges when applying these guidelines to pediatric patients (8, 12).

Purpose of Alert

Alerts associated with AKI serve different purposes depending on the data used to inform the notification and the criteria used to trigger the alert. In particular, some AKI alerts have been designed to identify patients at risk for AKI while others are designed to detect patients currently with AKI (13–15).

Identification of Patients at Risk of AKI

The 22nd ADQI emphasized identifying populations at risk of AKI, which can include a baseline set of risk factors including age, medications, baseline creatinine, and a problem list (12). As most pediatric patients inherently have few of these risk factors, efforts in detecting children at risk for AKI have focused on the initiation of nephrotoxic medications. Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) is an ongoing prospective quality improvement project that works to reduce nephrotoxic medication-associated AKI among non-critically ill hospitalized children (12). It involves systematic EHR screening and a decision support process (trigger report). This trigger report is reviewed by pharmacists who recommend daily serum creatinine monitoring in the exposed patients. Upon implementation, it was successful in reducing the number of AKI days per 100 days by 42% in its first year (13), and has since been shown to maintain a 23.8% decrease in AKI rates when incorporated across nine pediatric institutions (16). Risk prediction models have been specifically designed for pediatric patients which incorporate data beyond nephrotoxic agents. Implementation of an AKI risk prediction tool by Driest el al. resulted in increased screening for AKI *via* measurement of serum creatinine in a pediatric intensive care unit (17).

More recently, artificial intelligence and machine learning methods have made it possible to design algorithms to predict future episodes of AKI. Tomašev et al. developed a model for the prediction of AKI using a dataset of more than 700,000 patients from the United States Department of Veterans Affairs (18). Their model was able to predict 55.8% of all inpatient episodes of AKI and 90.2% of all AKI that required subsequent dialysis up to 48 h before they occurred. Sandokji et al. developed a machine learning algorithm that selected 10 factors to predict AKI within a 48-h window specifically in pediatric patients as well as the neonatal population (19). More data on these predictive algorithms and their effect on patient outcomes will be seen in the coming years (20).

Identification of Patients With AKI

Most alerts are designed to trigger based on the definition of AKI by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (21). AKI is defined in stages of increasing severity by a rising serum creatinine from baseline or declining urine output (UOP). Urine output is a simple and sensitive measure of kidney function (22). In the neonatal population, defining AKI by urine output captures more diagnoses than using serum creatinine alone (23). Inconsistent intake and output documentation in the electronic medical record, however, limits the use of UOP as a trigger for alerts. While serum creatinine is a reasonable biomarker to represent a patient's glomerular filtration rate in most cases, creatinine-based alerts alone can produce a false positive rate as high as 30% (24). The recent 23rd ADQI (25) emphasized the utility of incorporating additional injury biomarkers to these systems to select patients most likely to benefit from AKI-specific interventions, but recognize that many of these biomarkers still require clinical validation before widespread use.

Components of the Alert

The 15th Acute Dialysis Quality Initiative workgroup summary discusses the characteristics of an optimal alert, considering the technological as well as human factors impacting the implementation and efficacy of an electronic alert (8–10). At minimum, the content of the alert should include patient identification, the data used to trigger the alert, and the stage of AKI if available. The alert should occur as close to the time of AKI onset as possible. Some alerts target the primary contact for the patient directly whereas other alerts are displayed in the EHR for any provider with access. Alerts may be passive with no acknowledgment of receipt, or interruptive where a series of actions are required to dismiss the alert or proceed with additional orders.

Responses to the Alert

While e-alerts have been shown to improve the recognition of AKI, they have not consistently translated into improved outcomes of patients with AKI (15, 26). It has been proposed that alerts should be accompanied by a bundle of diagnostic and therapeutic interventions to prevent further injury. The 22nd ADQI emphasized that every exposure to risk factors associated with AKI, as well as episodes of AKI itself, should be followed by a kidney health response, also called a care bundle (12). Many of these care bundles incorporate the best practices in response to kidney injury in a simple and easy to remember mnemonic (**Table 1**). While they vary slightly depending on the context of their use, most include similar themes of fluid and blood pressure management, medication review, and the evaluation of urine (31).

USE OF AKI ALERTS IN ADULTS

The utilization of AKI alerts and its impact on clinical outcomes has been studied in a number of settings throughout the years. **Table 2** provides a summary of key publications studying the implementation of AKI alerts, selected from a literature review using the key words "AKI," "electronic alert," and "clinical decision support system." Early studies looked at the impact on e-alert implementation in the recognition of AKI and were helpful in understanding the epidemiology of AKI within the hospital population (41, 42). A study out of Ghent University Hospital by Colpaert et al. (43) was one of the first to report positive

TABLE 1 | Care bundles for acute kidney injury.

Name	Contents
4 Ms (12)	Medication adjustment
	Minimize exposure
	Message care team and patient
	Monitor
ABCDE (27)	Address drugs
	Boost blood pressure
	Calculate fluid balance
	Dip urine
	Exclude obstruction
AEIOU (6)	Assess cause of AKI
	Evaluate drug doses
	Intake and output charting
	Optimize volume status
	Urine dipstick
AUDITS (28)	Assessment
	Urinalysis
	Diagnosis
	Investigations
	Treatment
	Seek advice from nephrologist
KAMPS (12)	Kidney function check
	Advocacy
	Medications
	Pressure
	Sick day protocols
KDIGO care bundle for cardiac surgery patients (29, 30)	Avoidance of nephrotoxic agents
	Withhold ACEi and ARBs
	Close monitoring of SCr and urine output
	Avoidance of hyperglycemia
	Consider alternatives to radio-contrast agents
	Optimization of volume status and hemodynamic parameters
WATCH-ME for patients requiring dialysis (12)	Weight assessment
	Access
	Teaching
	Clearance
	Hypotension
	Medications

clinical outcomes following an automated AKI alert, reporting a significant increase in fluid intervention and a higher proportion of patients returning to baseline kidney function within 8 h of the alert.

The first randomized controlled trial on AKI alerts was conducted by Wilson et al. (15) at the University of Pennsylvania. In this single blind, parallel group trial, 1,201 adult patients were assigned to receive an AKI alert and 1,192 were assigned to the usual care group (21). There was no difference between the alert and usual care group in composite relative maximum change in creatinine, dialysis, and death at 7 days. There was no difference in the number of renal consults, number of nephrotoxic agents prescribed, no change in length of stay, and no change in number of creatinine lab measurements within 7 days (15, 44). Interestingly, a secondary analysis of this clinical trial using uplift modeling identified patients who might benefit most from AKI alerts. These were patients at risk of a more slowly developing AKI, including older patients, women, and those with a lower baseline creatinine (45). While pediatric patients were not included in this study, they certainly fall into this category.

Among the largest studies on AKI alerts has been the work of Holmes et al. and the Welsh AKI Steering Group (25, 26, 31, 41, 42). They employed a national AKI alert in a population of more than 3 million people in the hospital as well as the primary care setting. The Wales Laboratory Information Management System tracks creatinine values on patients in real time and an alert is issued according to the KDIGO AKI criteria. Over the course of 4 years, they found that the majority of adult AKI alerts were community acquired (53.5%) vs. hospital acquired (29.3%) and the rest (17.2%) were undetermined (25). They were also able to provide nationwide characterization of AKI in various clinical settings and report the true incidence of AKI in Wales.

Subsequent studies have looked at the impact of pairing the AKI alert with an actionable intervention on clinical outcomes. In the PrevAKI study, Meersch et al. (29) assessed the efficacy of a care bundle based on KDIGO guidelines to prevent cardiac surgery-associated AKI in high-risk patients. Patients were randomized to receive usual care or the KDIGO bundle, which included guidelines for managing volume status, hemodynamics, nephrotoxic agents, and hyperglycemia prevention (**Table 1**). They found a significantly reduced rate of AKI within 72 h after surgery, as well as improvement in hemodynamic parameters and severity of AKI. There were no changes to dialysis requirements, hospital length of stay, or adverse events related to the kidney.

Kolhe et al. (28) implemented an interruptive EHR alert at the Royal Derby Hospital which forced the provider to override or acknowledge the AKI care bundle. The care bundle required completion before a new blood test or medication could be ordered. The care bundle was completed in 25% patients within 24 h, and case fatality was higher when the care bundle was not completed. With their alert, they found a significant improvement in mortality, less progression to higher AKI stages, and lower odds of death at discharge (40). This study later expanded to the Tackling AKI study, a large multi-center pragmatic stepped wedge cluster randomized trial (36). The interruptive alert was no longer used; instead an alert with the care bundle was displayed in the EHR and a phone call was made to the clinical site for patients with AKI stages 2 and 3. Across five UK hospitals, results were significant for an increase in documentation of AKI. While there were no changes in 30-day mortality, there were improvements in medication optimization, fluid assessment, hospital length of stay, and quality of care (37). One of the reasons cited for the lackluster performance of clinical decision support systems (CDSS) in AKI is the difficulty in achieving effect sizes. Al-Jaghbeer et al. implemented a CDSS for AKI in a large regional health care system (38). They looked at $>$ 500,000 total patients, 12 months before ($n = 181{,}696$) and

TABLE 2 | Studies on acute kidney injury alerts.

References	Design	*N*	Setting	Baseline creatinine definition	E-alert type	Intervention	Key findings
Pediatric							
Menon et al. (6)	Prospective non-randomized	239 AKI alerts in 225 patients	Inpatients (non-ICU) aged 6 mo to 18 yo at Seattle Children's Hospital	Lowest in 6 months prior to admission or eCCl 120 mL/min/1.73 m^2	Page to primary provider	AEIOU care bundle	• Increase in AKI documentation, adjustment in medications and fluids • Higher eGFR at discharge and follow-up
Gubb et al. (32)	Prospective	2,472 AKI alerts in 1,719 patients	Inpatients ≥ 25 d-old and <18 yo in Wales	eCCl 120 ml/min/1.73 m^2 or midpoint normative creatinine value for age and sex	Displayed in EHR alongside lab result	None	• Higher 30-day mortality in HA- AKI vs. CA-AKI • Repeated AKI episodes associated with increased 30-d mortality and residual renal impairment
Holmes et al. (33)	Prospective	1,343 AKI alerts	Inpatients and outpatients aged < 18 yo in Wales	eCCl 120 ml/min/1.73 m^2 or midpoint normative creatinine value for age and sex	Displayed in EHR alongside lab result	None	• Greater number of HA-AKI vs. CA-AKI • Improved rate of renal recovery for hospitalized patients
Adult							
Wilson et al. (34)	Multicenter, randomized, double blind	3,059 patients in intervention group, 2,971 in usual care group	Inpatient units of 6 hospitals	Lowest in 7 days prior to admission	Pop-up window on EHR	Link to AKI orderset and option to add AKI to problem list	• Overall no change in progression of AKI/death/dialysis • Better AKI documentation • Increased mortality in non-teaching hospitals
Holmes et al. (35)	Prospective	193,838 AKI alerts in 132,599 patients	Inpatient and outpatients >18 yo in Wales	Lowest in last 7 days (HA-AKI) or last 8–365 days (CA-AKI)	Displayed in EHR alongside lab result	None	• Increase in AKI incidence (particularly community-based AKI) • Earlier AKI detection • Improvement in overall mortality
Selby et al. (36)	Multicenter stepped wedge cluster randomized	10,017 AKI alerts	All hospitalized patients >18 yo in five United Kingdom hospitals	Lowest in last 7 days or median of values in prior 8–365 days	Displayed in EHR and phone call to clinic site for AKI stage 2 and 3	AUDITS care bundle	• Increase in AKI documentation, fluid assessment and adjustment in medications • Decrease in hospital length of stay • No change in 30-d mortality
Park et al. (37)	Prospective	1,739 AKI patients after alert implementation	Non-nephrology inpatients in a tertiary referral hospital in Korea	Lowest within 2 weeks or first measured during hospitalization	Pop-up window on EHR	Automatically generated nephrology consult	• Decrease in overlooked and severe AKI events • Increase in nephrology consultation and AKI recovery • No change in mortality
Meersch et al. (29)	Randomized control trial	138 patients in intervention group, 138 patients in control group	Patients undergoing cardiac surgery with CPB at University of Muenster	None; high risk of AKI defined as TIMP2*IGFBP7 ≥0.3	None	KDIGO care bundle for cardiac surgery patients	• Reduction in AKI incidence first 72 h after surgery • Improved hemodynamics • Reduction in rate of moderate-severe AKI

(Continued)

TABLE 2 | Continued

References	Design	*N*	Setting	Baseline creatinine definition	E-alert type	Intervention	Key findings
Al-Jaghbeer et al. (38) and Bataineh et al. (39)	Prospective	346,412 AKI patients after alert implementation	All inpatients admitted to adult hospitals within University of Pittsburgh Medical Center system	Lowest in prior 12 months or back-calculation from normal eCCl	Displayed in EHR	Prompt to consult nephrology or ICU	• Decrease in hospital mortality rate, hospital duration and dialysis use • Decrease in nephrotoxic antibiotic use
Kolhe et al. (40)	Prospective observational	1,291 AKI patients after alert implementation	All inpatients > 18 yo at the Royal Derby Hospital	Lowest in last 7 days or median of values in prior 8–365 days	Interruptive alert on EHR requiring acknowledgment	AUDITS care bundle	• Improved mortality • Less progression of AKI • Lower odds of death at discharge.
Wilson et al. (15)	Single blind parallel group randomized control trial	1,201 patients in AKI alert group and 1,192 patients in usual care group	All inpatients > 18 yo at the University of Pennsylvania hospital	Lowest in prior 7 days	Page or email to primary provider	Link to external website with KDIGO AKI practice guidelines	• No change in dialysis requirement, nephrology consults, hospital length of stay

AEIOU, assess cause of AKI, evaluate drug doses, intake and output charting, optimize volume status, urine dipstick; AKI, acute kidney injury; AUDITS, assessment, urinalysis, diagnosis, investigations, treatment, seek advice from nephrologist; CA-AKI, community-associated AKI; CPB, cardiopulmonary bypass; eCCl, estimated creatinine clearance; EHR, electronic health records; HA-AKI, hospital-associated AKI; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes.

24 months after ($n = 346,412$) alert implementation. The system alerted clinicians on "possible AKI" based on the KDIGO SCr criteria. It also provided information on the reference creatinine used, stage of AKI, and a prompt to consult nephrology or intensive care. In comparing pre- vs. post-alert implementation, they found that mortality rate decreased from 10.2 to 9.4% after alert implementation, and there was a decrease in length of stay from 7.2 to 6.0 days for patients with AKI. A 2-year follow-up study on an additional 337,433 patients demonstrated sustained decrease in mortality rate and length of stay, as well as a significant decrease in the use of nephrotoxic agents (39).

More recently, Wilson et al. looked at e-alerts for AKI in 6,030 patients in a double blinded, parallel, randomized controlled trial across six centers (34). In the electronic health record alerts for acute kidney injury (ELAIA-1) study, they found that patients randomized to alerts were more likely to receive intravenous fluids, get a urinalysis or repeat SCr measured, and have documentation of AKI. There was however no difference in their primary outcome, which was a composite of AKI progression, receipt of dialysis, or death. Interestingly, there was a heterogeneity of treatment effect across the different hospitals. In the non-teaching hospitals in the study, patients in the alert arm were more likely to have met the primary outcome [relative risk (RR) 1.49, 95%CI 1.12–1.98].

PEDIATRIC AKI ALERT STUDIES

The studies discussed above focused on the adult population. Only a few studies have looked at implementing AKI alerts in pediatric patients (**Table 2**). The Welsh AKI group studied AKI alerts in pediatric patients in both the hospital and community setting (33). Over a period of 30 months, they reported a total of 2,087 alerts, corresponding to 1,343 incident episodes of AKI, of which 468 occurred in neonates. Hospital-acquired AKI accounted for 40.1%, community-acquired AKI accounted for 29.4%, and the rest was unclassified. They reported an incidence rate of pediatric AKI at 1.37 cases per 1,000 person-years.

A prospective study at Seattle Children's Hospital by Menon et al. (6) aimed to determine whether an AKI alert paired with a standardized care pathway would improve AKI detection and renal outcomes. This study included 239 unique AKI alerts with most being stage 1 AKI (68.6%) and 47% were defined as hospital-acquired AKI. With the alert intervention, this study found a significant increase in AKI documentation, intake and output charting as well as adjustments to fluid and medications. While there was a trend toward decreases in AKI stage, this finding was not statistically significant. Larger multi-center studies with greater longitude will be necessary to better understand the impact of AKI alerts on pediatric patients.

LIMITATIONS

There are limitations in the implementation of AKI alerts, some of which are unique to pediatric patients. Addressing these alerts in future studies may improve their efficacy and interpretability.

Accuracy of the Alert

The definition of AKI is highly dependent on the reliability and accuracy of information presented in the EHR. Unfortunately, urine output is not documented frequently or accurately enough to use for AKI alerts and a patient's baseline creatinine often does not exist in the medical record. Studies have used different methods to ascertain the baseline serum creatinine (SCr), including using the admission SCr, a pre-admission outpatient creatinine, or nadir inpatient SCr. There are concerns with all methods. For example, if a patient has community-acquired AKI, the admission SCr is likely to be higher than the patient's true baseline resulting in underdiagnosis of AKI (46). An additional issue in pediatrics is that the baseline kidney function evolves as a child grows. This is particularly challenging in neonates as their creatinine at birth is reflective of their mother's kidney function. Using the KDIGO definitions overestimated neonatal AKI in the study done by Holmes et al. (33), and the authors recommend using a serum creatinine >0.5 mg/dl as a threshold for AKI. While imperfect, the most common solutions to calculating baseline creatinine in pediatrics are to estimate baseline SCr including back-calculation based on eGFR of 120 ml/min per 1.73 m^2 or use a normative midpoint value for age (33, 47).

Type of Alert

For an alert to work, it must be noticed. Much research has been done on the balance between intrusive and passive alerts and their relative efficacy (7). Providers are more likely to act on an interrupting alert that forces an action. However, if these intrusive alerts are too frequent or disproportionately associated with false positives, all alerts of the same type are more likely to be dismissed without action (48, 49). Improperly implemented alerts can lead to alert fatigue, which may further affect the efficacy of the alert. When considering how to deliver an alert to maximize patient benefit while also reducing alert fatigue, applying alerts only to patients at high risk who may gain most from intervention would be a potential solution (49). Alerts could also be targeted at providers working directly with the patient in question at the time of potential error, such as when nephrotoxic agents are ordered.

Interventions Associated With Alert

Care bundles have been recommended and used with e-alerts as an attempt to improve the outcomes associated with AKI (6, 28, 29, 38, 40). Currently, care bundles include general common sense measures such as optimal fluid management, medication review, and urinalyses (**Table 1**). However, as seen in the ELAIA-1 study (34), care bundles that do not provide patient specific recommendations may not be helpful, and have the potential to cause more harm. Additional research is needed on this aspect of CDSS.

CONCLUSIONS

As a tool that is able to detect patients with AKI, electronic alerts meet the need for identifying patients at high risk for poor outcomes. Criticism of existing studies on AKI alerts note that little impact on overall mortality has been seen with the implementation of alerts. However, a higher level of care is consistently provided to patients after AKI alerts were triggered, particularly when bundled with resources of a care plan. Patients with AKI alerts also benefited from detailed documentation of AKI diagnoses, closer attention to fluid and medication management, and the involvement of nephrology providers. This comprehensive level of care that occurs with an automatic real-time notification has few downsides. For pediatric patients in particular, these simple interventions can be an effective resource to reduce the burden of AKI on our communities and hospitals.

AUTHOR CONTRIBUTIONS

EN and SM contributed equally to the conception and design of the manuscript, drafted the article and made critical revisions related to the intellectual content of the manuscript, and approved the final version of the article to be published. All authors contributed to the article and approved the submitted version.

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A Precision Medicine Approach to Biomarker Utilization in Pediatric Sepsis-Associated Acute Kidney Injury

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Sepsis is a leading cause of morbidity and mortality in critically ill children, and acute kidney injury (AKI) is a frequent complication that confers an increased risk for poor outcomes. Despite the documented consequences of sepsis-associated AKI (SA-AKI), no effective disease-modifying therapies have been identified to date. As such, the only treatment options for these patients remain prevention and supportive care, both of which rely on the ability to promptly and accurately identify at risk and affected individuals. To achieve these goals, a variety of biomarkers have been investigated to help augment our currently limited predictive and diagnostic strategies for SA-AKI, however, these have had variable success in pediatric sepsis. In this mini-review, we will briefly outline the current use of biomarkers for SA-AKI, and propose a new framework for biomarker discovery and utilization that considers the individual patient's sepsis inflammatory response. Now recognized to be a key driver in the complex pathophysiology of SA-AKI, understanding the dysregulated host immune response to sepsis is a growing area of research that can and should be leveraged to improve the prediction and diagnosis of SA-AKI, while also potentially identifying novel therapeutic targets. Reframing SA-AKI in this manner – as a direct consequence of the individual patient's sepsis inflammatory response – will facilitate a precision medicine approach to its management, something that is required to move the care of this consequential disorder forward.

Keywords: sepsis, acute kidney injury, biomarkers, precision medicine, enrichment

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INTRODUCTION

Sepsis is common in the pediatric intensive care unit (PICU), accounting for 75,000 hospitalizations annually in the United States (1). Children with sepsis suffer substantial morbidity and mortality, and those risks are further increased by the co-incidence of acute kidney injury (AKI), a frequent complication of pediatric sepsis (2, 3). Impacting almost half of critically ill children who meet criteria for severe sepsis (4), sepsis-associated AKI (SA-AKI) has been associated with poor outcomes including prolonged lengths of stay, higher mortality, and increased healthcare costs (3, 5, 6). Unfortunately, despite the burden it imposes on health outcomes, there are currently no effective disease-modifying therapies for SA-AKI once present (7, 8). As a result, therapeutic approaches are centered on prevention and supportive care, including employment of renal protective measures and timely initiation of renal replacement therapy, if indicated (9, 10).

A primary limitation to the successful development of novel therapies to treat SA-AKI is an incomplete understanding of the pathophysiology. Historical perspectives considered SA-AKI to be the result of renal hypoperfusion during the shock state, leading to acute tubular necrosis (11). However, the modern pathophysiologic model of SA-AKI recognizes a much more complex and heterogeneous disease – a combination of a dysregulated host inflammatory response to infection, altered microcirculatory blood flow, and metabolic derangements that ultimately lead to cell cycle arrest and apoptosis of renal tubular epithelial cells (12, 13). Difficulties in treatment development encountered due to this complexity are further exacerbated by the limited diagnostic strategies for SA-AKI, as it is now well-established that serum creatinine and urine output – the current gold standards for diagnosis – are fraught with issues, particularly among patients with sepsis (14). Indeed, the limitations of these tools are highlighted by the recent 23rd Acute Dialysis Quality Initiative recommendations, which suggest incorporating tubular injury biomarker status into the definition of AKI, when available (15). Taken together, the lack of precision diagnostics for SA-AKI, coupled with a limited understanding of the individual heterogeneous pathophysiology, have prevented advances in therapy beyond our current standards of prevention and supportive care (16).

With these issues in mind, it is not surprising that there is a growing interest in identifying biomarkers for SA-AKI. In addition to the clear need for validated injury biomarkers to improve diagnostic precision once present, biomarkers that allow for early identification of patients at risk for severe, persistent SA-AKI and those that reflect the patient-specific underlying pathophysiology are needed, as they might allow for prompt implementation of renal protective strategies, identification of biologically important targets for development of novel therapies, and provide a mechanism for enrichment of future clinical trials (17). Given the complexity of SA-AKI outlined above, it is unlikely that one biomarker measured at one moment in time will be able to achieve these goals, and this reality should inform our approach to identifying and employing biomarkers for SA-AKI.

This mini-review proposes a new framework for the discovery and utilization of biomarkers for SA-AKI. The foundational premise is that the pathophysiology of SA-AKI is directly tied to an individual's unique sepsis-related inflammatory response, and thus the diagnostic and treatment approach to SA-AKI may be different from other forms of AKI. Within this framework, we will briefly describe the current state of biomarkers for SA-AKI and discuss their limitations. We will then evaluate how biomarkers have been employed for the identification of individual sepsis molecular signatures, and how these may be leveraged in SA-AKI. Ultimately, if biomarkers can be biologically linked to the dysregulated inflammatory response to sepsis, then a precision medicine approach to the diagnosis and treatment of SA-AKI can be utilized to improve patient outcomes.

THE CURRENT APPLICATION OF BIOMARKERS IN SEPSIS-ASSOCIATED AKI

To date, a variety of biomarkers for SA-AKI have been studied. The biological underpinnings of these biomarkers vary, and include direct markers of tubular injury, regulatory proteins responsible for promoting cell cycle arrest, and more recently, proteins involved in the inflammatory cascade induced by sepsis (18, 19). Thus, far, SA-AKI research utilizing biomarkers has been limited to improving diagnostic and predictive capacity, most with modest success (18). Importantly, there have been no interventional trials to date utilizing biomarkers to initiate disease-specific therapy in SA-AKI. An overview of the biomarkers that have been most widely investigated in SA-AKI is included in **Table 1**.While the purpose of this review is not to cover these previously studied biomarkers of SA-AKI in detail, two deserve more in depth discussion.

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

As the most widely studied biomarker of AKI, NGAL – a protein produced by the injured nephron that can be measured in both urine and serum – has also been studied extensively as a biomarker of SA-AKI (37). While NGAL has been shown to successfully identify patients with AKI secondary to a variety of etiologies (38–40), its utility in sepsis is less clear (41–44). This is in large part due to an increase in systemic NGAL production – namely by neutrophils and the liver – as part of the inflammatory response to infection, independent of injury to nephrons (20). The consequence of this lack of kidney-specific production of NGAL has been modest performance when utilized for diagnosis and prediction of SA-AKI, often with high sensitivity but poor specificity (**Table 1**) (21, 22). Unfortunately, difficulty disentangling the fraction of NGAL elevation that is attributable to AKI, vs. a more generic systemic inflammatory response among patients with sepsis, likely limits its utility as a single biomarker for the diagnosis of SA-AKI, although more study is warranted.

Cell Cycle Arrest Markers

The induction of cell cycle arrest in renal tubular epithelial cells plays an important role in the early pathophysiology of all forms of AKI (11). Consequently, the expression of cell cycle arrest proteins tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) have been shown to be increased in renal tubular cells in response to stress or injury (18, 25). The combination of TIMP-2 and IGFBP7 for the prediction of AKI in high risk patients has been examined in several landmark studies (**Table 1**) (26, 28, 45), and is now approved by the U.S. Food and Drug Administration for critically ill adults with one or more risk factors for AKI, including sepsis (25). In adults with sepsis, this tool (known as NephroCheck®) demonstrated an area under the receiver

TABLE 1 | Investigated biomarkers of sepsis-associated acute kidney injury.

Biomarker	Site of production	Function	Pathophysiology	Measured	Potential applications in SA-AKI	Time to AKI	Limitations
Neutrophil gelatinase-associated lipocalin (NGAL)	Systemic: liver, circulating neutrophils, epithelial cells	Binds bacterial siderophores to inhibit growth; also has anti-apoptosis effects and enhances proliferation of renal tubules (20)	Marker of renal tubular epithelial injury and systemic inflammation (20)	Plasma, Urine	Plasma NGAL within 24 h of admission predicted SA-AKI in children with an AUROC of 0.68 (21)	AKI diagnosed by day 7 (median 1, range 1–6) (21)	High sensitivity with poor specificity
	Kidney: proximal tubule, thick ascending limb of Henle's loop, distal tubule, and collecting duct				Meta-Analysis: plasma NGAL predicted SA-AKI with an AUROC of 0.86, and urine NGAL with an AUROC of 0.90 (22)		Elevated in the setting of systemic inflammation
Kidney injury molecule-1 (KIM-1)	Kidney: tubular apical transmembrane protein, soluble form excreted in urine	Involved with repair of renal tubular epithelial cells (23)	Upregulated during ischemic and nephrotoxic AKI (23)	Urine	Increased within 6–24 h of admission in patients with SA-AKI. Level at 24 h predicted SA-AKI with an AUROC of 0.91 (24)	AKI diagnosed by 48 h (24)	Limited investigations in pediatric SA-AKI
Netrin-1	Systemic: nervous system, heart, lung, liver, intestines, blood vessels Kidney: secreted by proximal tubule epithelial cells, present in renal microvascular endothelial cells	Axon guidance molecule, inhibits leukocyte migration, promotes endothelial chemoattraction (18)	Increased production in renal tubular epithelial cells in response to ischemic AKI (18)	Urine	Levels peaked early, within 3-6 h of admission, in patients SA-AKI. Level at 3 h predicted SA-AKI with an AUROC of 0.86 (24)	AKI diagnosed by 48 h (24)	Limited investigations in pediatric SA-AKI
Tissue inhibitor of metalloproteinase-2 (TIMP-2)	Renal tubular epithelial cells	Promotes G1 cell cycle arrest via increasing p27 expression (25)	In response to tubular epithelial damage, TIMP-2 and IGFBP7 expression is increased to initiate cell cycle arrest and signal to neighboring cells via paracrine and autocrine modalities (26)	Urine	Product of urine TIMP-2 · IGFBP7 predicts SA-AKI within 12 h of admission with an AUROC of 0.84 (27) Now available as FDA approved tool known as NephroCheck® in adults with one or more AKI risk factors, including sepsis (27)	AKI diagnosed within 12 h of study enrollment (28)	Limited study in children, FDA approval does not apply to patients <18 years old
Insulin-like growth factor-binding protein 7 (IGFBP7)	Renal tubular epithelial cells	Promotes G1 cell cycle arrest via increasing expression of p53 and p21 (25)					
Soluble triggering receptor expressed on myeloid cells 1 (sTREM-1)	Systemic: expressed by neutrophils and monocytes	TREM-1 triggers secretion of pro-inflammatory mediators in response to extracellular bacterial infections (29). sTREM-1 is a soluble form of TREM-1 that modulates cytokine production to prevent hyper-responsive inflammatory cascade (30)	Plasma sTREM-1 levels strongly correlate to sepsis severity (31). It may be filtered into the urine, or produced and excreted locally during acute tubular necrosis (32)	Plasma, Urine	Plasma sTREM-1 predicted SA-AKI with an AUROC of 0.746 and urine sTREM-1 with an AUROC of 0.778 24-h prior to diagnosis by SCr (33)	AKI diagnosed by day 7 (median 2, range 1–7) (33)	No prospective studies in pediatric SA-AKI

(Continued)

TABLE 1 | Continued

Biomarker	Site of production	Function	Pathophysiology	Measured	Potential applications in SA-AKI	Time to AKI	Limitations
	Kidney: endothelial cells, tubular epithelial cells, infiltrating inflammatory cells				Urine sTREM-1 increased 48-h prior to SA-AKI in adults (34)		
Interleukin-18 (IL-18)	Systemic: secreted by macrophages after precursor is cleaved by caspase-1 intracellularly	IL-18 is a proinflammatory cytokine that induces interferon gamma production from natural killer cells, also induces T-cells to produce interleukin-17 (35)	IL-18 is released by renal tubular cells in response to injury and is thought to mediate acute tubular necrosis (36)	Urine	Urinary 1L-18 increased 24–48 h prior to diagnosis of AKI in adult patients with Acute Respiratory Distress Syndrome and AKI. IL-18 demonstrated an AUC of 0.73 to predict AKI in the next 24 h (36)	AKI diagnosed by day 6 of hospitalization. Biomarker values reported 24 h prior to time AKI was diagnosed	No studies in children, less specific to acute kidney injury
	Kidney: released in response to tubular injury						

AKI, acute kidney injury; SA-AKI, sepsis-associated acute kidney injury; AUROC, area under the receiver operating curve; FDA, Food and Drug Administration; TREM-1, triggering receptor expressed on myeloid cells 1; SCr, serum creatinine.

operating curve (AUROC) of 0.84 for the prediction of SA-AKI, and its predictive performance significantly improved via the addition of a clinical prediction model (AUROC of 0.94) (27). The use of NephroCheck® to assess the impact of directed implementation of standardized renal protection strategies compared to standard of care in patients with septic shock will be assessed in the upcoming Limiting AKI Progression in Sepsis (LAPIS) Trial (NCT04434209) (46). Unfortunately, this tool has not been studied robustly nor been validated in children.

As noted above and in **Table 1**, there are several limitations to the use of these biomarkers in pediatric SA-AKI. First and foremost, the data for their use in pediatric sepsis is scare, and this is especially problematic given a growing host of literature to suggest fundamental differences in the sepsis inflammatory response – and thus, the risk of SA-AKI – based on age (47–50). Furthermore, the biologic action of many of these biomarkers appear to be non-specific to sepsis (38, 51, 52), thereby providing no information regarding the patient's underlying inflammatory state, which is likely necessary to identify effective, patient-specific therapies for SA-AKI. Taken together, these realities suggest that additional approaches to biomarker discovery and utilization is required.

THE SEPSIS MOLECULAR SIGNATURE AND ITS ROLE IN SEPSIS-ASSOCIATED AKI

As outlined above, sepsis is a complex syndrome that stems from a dysregulated host immune response to an infectious trigger, and is a leading cause of death and disability in critically ill children (53). Given these consequences, substantial resources have been focused on improving the care of patients with sepsis, however, these efforts have failed to produce meaningful therapeutic advances beyond the mainstays of supportive care and antibiotics (54). Failures are undoubtedly tied to the heterogeneity of the disease expression on the individual patient level (17). As such, attempts to resolve this heterogeneity by identifying the sepsis molecular signature of a patient are becoming more common, as successful strategies for doing so could allow for more targeted employment of therapies (55–61).

This concept of separating a heterogeneous group of patients into more homogenous subgroups to guide management is termed *enrichment*, a fundamental tenant of precision medicine (62). *Prognostic enrichment* refers to selecting a subgroup of patients who share a similar likelihood of suffering an outcome of interest, such as mortality, while *predictive enrichment* selects a subgroup who are more likely to respond to a particular therapy based on underlying biology (63). This general concept, and how it may be employed to direct a precision medicine approach to SA-AKI therapy, is depicted in **Figure 1**.

In pediatric sepsis, *prognostic enrichment* strategies have been used to develop a set of serum biomarkers – known as the Pediatric Sepsis Biomarker Risk Model (PERSEVERE) – capable of reliably assigning baseline risk of 28-day mortality

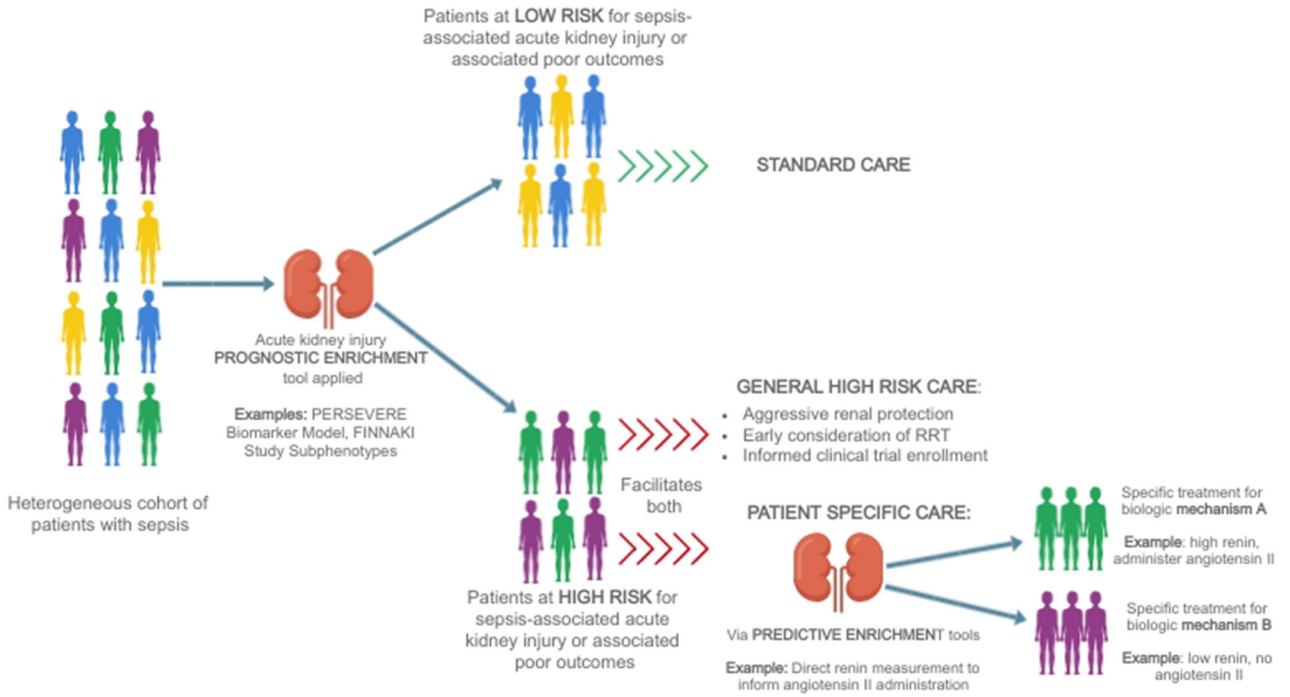

FIGURE 1 | A heterogeneous group of patients with sepsis is divided first using a prognostic enrichment tool into those at high and those at low risk of sepsis-associated acute kidney injury [for example, the PERSEVERE Biomarker Model (64)] or associated poor outcomes such as delayed renal recovery or mortality [for example, FINNAKI Study subphenotypes (65)]. Patients who are at low risk may be treated with standard therapy, while patients at high-risk may receive more aggressive care aimed at renal protection, earlier consideration of renal support in the form of renal replacement therapy, and be considered for informed enrollment in clinical trials aimed at identifying therapies for sepsis-associated acute kidney injury. Ultimately, the goal is to utilize predictive enrichment tools to further subdivide patients on the basis of biology [for example, using direct renin levels to inform the use of angiotensin II (66)], allowing for the implementation of patient-specific therapies.

(67). This model incorporates five serum protein biomarkers measured in the first 24 h of septic shock that were originally identified utilizing discovery-oriented genome-wide profiling of children with septic shock (68, 69), and then narrowed further using classification and regression tree (CART) modeling for estimation of baseline mortality risk (67). An updated version of the model (PERSEVERE-II) incorporates platelet count, and has been recently prospectively validated for the prediction of mortality (70). Similarly, *predictive enrichment* has also been utilized to subgroup patients based on gene expression, which led to the identification of two distinct endotypes that may require different treatment approaches (58). For example, one particular endotype – endotype A – is associated with increased repression of genes that regulate adaptive immunity and glucocorticoid receptor signaling, and patients with this endotype have demonstrated an increased mortality rate when treated with corticosteroids (71, 72). This association between endotype A and poor outcome in response to corticosteroids was recently corroborated among adults with septic shock (73). Given our current understanding of the significant role that the host inflammatory response plays in the pathophysiology of SA-AKI (12, 13), it is reasonable to consider leveraging this pediatric sepsis enrichment work to improve the care of SA-AKI, a similarly heterogeneous disorder (11, 12).

THE GOAL: SEPSIS-SPECIFIC BIOMARKERS FOR A PRECISION MEDICINE APPROACH TO SEPSIS-ASSOCIATED AKI

A precision medicine approach to SA-AKI will require both prognostic enrichment tools to identify high risk patients early and accurately, and predictive enrichment tools to deliver the right treatment to the right patient. Biomarkers play an important role in achieving these goals, however, we believe that a shift to include biomarkers of the dysregulated immune response to infection is prudent. Such a shift will also require a reframing of AKI in sepsis, recognizing that it is not simply "associated" with sepsis (as suggested by the term SA-AKI), but a disease state that is induced by the host inflammatory response. In this section, we will outline the current application of precision medicine to the study of SA-AKI within this framework, and highlight the remaining critical knowledge gaps.

Prognostic Enrichment Tools for SA-AKI

The first step to improving outcomes for patients with SA-AKI is early identification of those at highest risk. While sepsis is perhaps the most significant risk factor for AKI in critically ill patients, a significant proportion of patients with septic shock do

not develop AKI. Therefore, further delineation of an individual's risk profile via the development of prognostic enrichment tools is required. To date, few validated prognostic enrichment strategies for SA-AKI that incorporate sepsis-specific biomarkers exist, as outlined below.

Leveraging work done in the more advanced field of sepsis precision medicine, researchers have utilized "omic" technologies (notably genomics, transcriptomics and proteomics) to identify patients at high risk for persistent SA-AKI (10, 64, 74). Using microarray technology to study SA-AKI related transcriptomics, one group retrospectively identified 21 candidate biomarkers for the prediction of SA-AKI based on the upregulation of mRNA gene probes in patients with persistence of severe SA-AKI at day 7 of septic shock (74). The expression pattern of these 21 upregulated genes were shown to predict the presence of this severe, persistent form of SA-AKI with high sensitivity (98%) and reasonable specificity (80%) (74). Results from this work informed a second study in which the protein products of five of the aforementioned 21 genes–elastase 2 (ELA2), fibroblast growth factor 13, matrix metalloproteinase 8 (MMP8), olfactomedin 4 (OFM4), and proteinase 3 (PRTN3) – were incorporated into a new CART-derived model to predict the presence of SA-AKI at day 3 of septic shock (10). The test characteristics of this model in the derivation cohort were robust, with an AUROC of 0.95; when tested in a validation cohort, the predictive capacity of the model remained reasonable with an AUROC of 0.82, which was superior to knowledge of AKI stage by serum creatinine on the day of septic shock development alone (AUROC 0.73) (10). Using a similar approach, a more recent study utilized the PERSEVERE biomarkers and AKI stage by serum creatinine on the day of admission to develop a model for prediction of severe SA-AKI at day 3. This model had similarly impressive test characteristics, with an AUROC of 0.95 (64). Unfortunately, while these models represent potentially feasible prognostic enrichment tools for SA-AKI, they have not yet been prospectively validated nor utilized to inform patient care, which represent areas of future study.

Another strategy incorporating biomarkers that has been utilized for prognostic enrichment in SA-AKI is latent class analysis (LCA). This approach allows for the incorporation of multiple variables– including comorbidities, clinical data and biomarkers – to allow for the identification of potential subphenotypes of heterogeneous disease states. Using this methodology, a recent *post-hoc* analysis of the FINNAKI Study described two subphenotypes of critically ill patients with SA-AKI who have significantly different rates of mortality and renal recovery (65). Patients categorized as subphenotype 2 – which was associated with increased mortality and decreased short-term renal recovery – demonstrated elevations in biomarkers associated with endothelial dysfunction and an overall increased inflammatory state. Interestingly, four of the significantly upregulated inflammatory biomarkers in subphenotype 2 (ELA2, OFM4, MMP8 and PRTN3) overlapped with the above mentioned AKI prediction model derived by Wong and colleagues (10). Using a similar approach, a second group also identified two SA-AKI subphenotypes (AKI-SP1 and AKI-SP2) via the application of LCA to a panel of 29 clinical and biomarker variables (75). This study similarly showed decreased survival and renal recovery in patients with upregulation of biomarkers associated with endothelial dysfunction and inflammation, although the included biomarkers differed. While these LCA-driven studies identified high-risk subphenotypes of patients already known to have SA-AKI, they represent potentially viable prognostic enrichment tools, specifically to help delineate patients most likely to benefit from enrollment in clinical trials, as well as from potentially high-risk and high-resource utilizing therapies such as renal replacement therapy (RRT).

Predictive Enrichment Tools for SA-AKI

The identification of predictive enrichment tools for SA-AKI–those that provide insight into the underlying pathophysiology and thereby reveal potential treatment strategies–remains an elusive goal. Predictive enrichment tools are particularly helpful in heterogeneous disease states, as they may identify subphenotypes of patients who might benefit from a specific, biologically-based therapy. While **Figure 1** outlines an ideal circumstance in which predictive enrichment occurs in an identified high risk subset of patients, it is important to note that the development and use of predictive enrichment tools does not necessarily rely on the availability of reliable prognostic enrichment strategies. However, the identification of effective predictive enrichment tools requires a deep understanding of the patient-specific pathophysiology, which remains a significant barrier in SA-AKI.

Thus far, the only proposed predictive enrichment strategy that is clinically feasible was elucidated via a series of *post-hoc* analyses of the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3), a clinical trial of adults with vasodilatory shock treated with angiotensin II (76). In these studies, the authors were able to demonstrate that patients who were treated with angiotensin II had improved 28-day survival and earlier discontinuation of RRT (77), and that these advantages were best seen in patients who had higher serum renin levels prior to angiotensin II administration, suggestive of sepsis-induced angiotensin converting enzyme deficiency (and thus angiotensin II deficiency) in the setting of endothelial injury (66). From these findings, the authors postulated that administration of exogenous angiotensin II to patients with vasodilatory shock may be beneficial beyond simply increasing blood pressure, as it was also demonstrated to normalize high renin levels, which have been known to be proinflammatory (66). Given that serum renin levels can be easily measured, this example of predictive enrichment can and should be applied prospectively in future studies examining the effect of angiotensin II on mitigation of SA-AKI.

CONCLUSION

SA-AKI is a common and consequential diagnosis in critically ill children, yet successful diagnostic and treatment strategies remain unacceptably scarce. In order to improve the care of patients with SA-AKI, researchers must move toward a precision medicine approach that considers the heterogeneity

of the disease on the individual patient level. While biomarkers will undoubtedly play an important role in these endeavors, the complex pathophysiology of SA-AKI requires that we consider the use of biomarkers specific to the individual sepsis inflammatory response, a key driver of renal injury in these patients. To do this, researchers must leverage and build upon existing sepsis precision medicine work, facilitating the development of prognostic and predictive enrichment tools that could advance the care of SA-AKI beyond prevention and renal support. A necessary and feasible first step in this process is the development and validation of reliable tools for the prediction of patients at highest risk for SA-AKI, as such a tool could facilitate the implementation of early and aggressive renal protection strategies, and perhaps more importantly in pediatrics, reduce the number of patients needed to study by informing enrollment in clinical trials aimed at identifying disease-modifying therapies. While the use of individual patient biology-driven therapies via predictive enrichment remains an elusive goal, reframing SA-AKI as a heterogeneous disease that will likely require an individualized approach to therapy is an important first step that should inform future research.

AUTHOR CONTRIBUTIONS

JO, NS, and HW were responsible for writing and editing this mini-review. All authors approved the final version for submission.

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REVIEW
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Impact of Acute Kidney Injury on Critically Ill Children and Neonates

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Acute kidney injury (AKI) is a clinical syndrome that manifests as an abrupt impairment of kidney function. AKI is common in critically ill pediatric patients admitted to the pediatric intensive care units. AKI is a deleterious complication in critically ill children as it is associated with increased morbidity and mortality. This review provides an overview of the incidence, morbidity, and mortality of AKI in critically ill children in general and specific cohorts such as post-cardiac surgeries, sepsis, critically ill neonates, and post stem cell transplantation.

Keywords: acute kidney injure, volume overload, critically ill children, neonatal intensive care unit, COVID-19

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INTRODUCTION

Acute kidney injury (AKI) refers to a clinical syndrome manifested as abrupt impairment of kidney function. Although the first systematic terminology and classification of AKI were not developed till 2002 by the Acute Dialysis Quality Initiative (ADQI) group, the clinical manifestations and the deleterious impacts of this syndrome were reported in ancient medical scripts. In his Aphorisms written sometime in 400 *BCE,* Hippocrates described oliguric kidney failure complicating a febrile illness and described the generalized edema as "leucophlegmatia," which means an overabundance of white phlegm as an attempt to interpret the cause of the white skin color seen in such edematous patients (1). Throughout history, researchers and clinicians gave this syndrome different terms, such as "ischuria renalis" in the 1800s, acute Bright's disease in the early 1900s, and "war nephritis" during the First World War (2, 3). However, the description of this syndrome was not based on a systematic approach till the "Risk, Injury, Failure, Loss, and End-Stage (RIFLE)" criteria were developed by the ADQI working group in 2004 in adults (4). Since then, the RILFE criteria were modified and refined to include more precise criteria and different terminology. In 2007, "pediatric" RIFLE criteria were adopted for children (5) and the acute kidney injury network (AKIN) working group added further criteria and modified the staging of AKI severity (6). Finally, a comprehensive definition and staging that take into consideration the previously described criteria were introduced by the Kidney Disease Improving Global Outcomes (KDIGO) in 2012 (3) as shown in **Table 1**.

This chapter provides an overview of AKI epidemiology in critically ill pediatric patients and its associated morbidity and mortality. Additionally, we looked into the epidemiology and outcomes of AKI in specific populations of critically ill children.

INCIDENCE OF AKI IN HOSPITALIZED CHILDREN

AKI is common in hospitalized pediatric patients with variably reported incidences ranging from 0.34% up to 5% in different studies (7, 8). It is more common in critically ill children than other hospitalized children, with a reported incidence of 30–50% (9, 10). This high incidence rate sets AKI as the commonest medical complication in critically ill pediatric patients admitted to pediatric intensive care units (ICU) (7).

TABLE 1 | The kidney disease improving global outcomes (KDIGO) definition and classification of acute kidney injury (AKI)*.

Definition		
1. Increase in sCr ≥ 0.3 mg/dl (≥26.5 μmol/L) within 48 h; OR		
2. Increase in sCr ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; OR		
3. UOP < 0.5 ml/kg/h for 6 h.		
AKI severity stages		
	Per sCr criteria	**Per UOP criteria**
Stage 1	1.5–1.9 times baseline OR	
	≥0.3 mg/dl (≥26.5 μmol/L) absolute increase.	<0.5 ml/kg/h for 6–12 h
Stage 2	sCr ≥ 2–2.9 times baseline	UOP < 0.5 ml/kg/h for ≥12 h
Stage 3	sCr ≥ 3 times baseline OR	
	Increase in sCr to ≥4 mg/dl (≥353.6 μmol/L) OR	
	Initiation of kidney replacement therapy OR,	
	In patients < 18 years, decrease in eGFR < 35 ml/min/1.73 m^2	<0.3 ml/kg/h for ≥24 h OR
	Anuria for ≥12h	

Adopted and modified from (3)
sCr, serum creatinine; UOP, urine output; eGFR, estimated glomerular filtration rate.

AKI rates increased 20-fold, from 0.5 to 9.9 cases per 1,000 hospitalized children between 1982 and 2004 according to a Thai study (11). The increase of the incidence is likely influenced by many factors such as the increased awareness of AKI as a common complication in the ICU population specifically after the evolution of systematic definitions of AKI. Additionally, the increased utilization of nephrotoxic medications (8–10, 12) and the advanced interventional and medical approaches to support critically ill children such as cardiopulmonary bypass (CBP) surgeries, extracorporeal membrane oxygenation (ECMO), solid organ, and stem cell transplantations could contribute to the increased incidence in of AKI.

The pathophysiology of AKI in critically ill patients is multifactorial. It varies in different areas of the world; it can occur secondary to kidney hypo-perfusion (e.g., cardiac dysfunction, hypotension, severe dehydration, bleeding, sepsis, or significant ascites impairing kidney perfusion), kidney tissue injury (secondary to prolonged impaired kidney perfusion or nephrotoxic medications) (10, 13–15), or less commonly due to primary kidney diseases like hemolytic uremic syndrome and glomerulonephritis in <10% of the cases (11, 16).

IMPACT OF AKI ON PEDIATRIC ICU POPULATION

Impact of AKI on ICU Population Collectively

The AWARE (Association Worldwide AKI Renal Angina and Epidemiology) study, published in 2017, comprehensively delineated AKI in children admitted to ICU. The (AWARE) study (17) is one of the most inclusive published studies in the epidemiology of AKI in critically ill children regardless of the underlying cause of ICU admission. This international observational study involved 32 pediatric ICU centers from the world, mainly from North America. The study enrolled more than 4,600 critically ill children from 3 months up to 25 years old. The study excluded patients with chronic kidney disease who have estimated glomerular filtration rate (GFR) of < 15 ml/min/1.73 m^2, patients on dialysis, kidney transplant patients admitted within 90 days of transplantation, patients admitted to ICU within 3 months following surgical correction of congenital heart disease, patients with uncorrected congenital heart disease, and patients post-cardiac catheterization. The authors reported AKI incidence using UOP or Cr KDIGO definition as 26.9% (95% CI: 25.6–28.2) during the first 7 days of ICU admission. 11.6% of critically ill children had severe AKI defined as stage II or stage III AKI using serum creatinine and/or urine output KDIGO criteria.

Severe AKI was a statistically independent risk factor for mortality after adjusting for the diagnosis at ICU admission, coexisting medical conditions, the severity of illness scores, and utilization of mechanical ventilation, vasoactive support, ECMO, and renal replacement therapy. The adjusted odds risk of mortality on day 28 of ICU admission was 1.77 in patients with severe AKI. Moreover, severe AKI was independently associated with other secondary outcomes such as increased kidney replacement therapy utilization, increased mechanical ventilation days, and ICU stay length.

In a *post hoc* analysis in the AWARE data (18), the authors highlighted the importance of utilizing both urine output and serum creatinine criteria to identify AKI. They found that isolated use of the creatinine criteria would have missed nearly a third of AKI cases as the creatinine-missed cases met only the KDIGO UOP definition portion. The 28-day mortality rate was similar for those who met stage II or III by only serum creatinine criteria (6.7%) and those who met stage II or III by only urine output criteria. Moreover, the mortality rate was much higher (38%) in those who met both criteria.

The majority of childhood AKI studies did not utilize the urine output criteria. This can be attributed mainly to the fact that the majority of critically ill children do not have good documentation

of urine output, as there is a general push back not to insert Foley catheters to prevent urinary tract infections. Even when a urinary catheter is inserted, AKI is usually hard to capture because the urine output is a dynamic measure that requires evaluation over different periods of time for which special programming in the electronic medical record systems is needed to be reliably captured. However, despite the challenges, oliguria remains a crucial component to recognize AKI as the drop in urine output should prompt evaluation of kidney function and more careful management of fluids and nephrotoxic agents.

Impact of AKI on Children With Congenital Heart Disease Undergoing Cardiac Surgery

AKI following post-cardiac surgery is a known complication in children undergoing cardiac surgery, mainly when utilizing CBP. Indeed, this cohort of critically ill children was the initial focus of childhood AKI research to understand the impact of the biomarkers on AKI. The timed and isolated risk factor of inducing AKI by applying the CBP made this cohort of patients the ideal cohort to study the consecutive pathological changes after initiating the bypass. A significant portion of the data and knowledge regarding the diagnostic utilities, such as the sensitivity and the positive predictive value of the novel tubular injury markers, were acquired by studying these biomarkers in this cohort. Cardiopulmonary bypass is associated with hypotension, impaired kidney perfusion, non-pulsatile perfusion, the release of inflammatory markers, kidney hypoxia, ischemia, and reperfusion injury and tissue damage secondary to oxidative stress; all of these factors contribute to developing AKI post-cardiac surgery (19, 20).

The incidence rate varies from one center to another, but most pediatric studies reported that 30–50% of children and up to 60% of neonates develop AKI after open-heart surgery (21–23). Many well-identified risk factors increase the risk of AKI following cardiac surgeries, such as low weight with the highest risk in the neonates and weight <5 kg, the complexity of the cardiac defect, high pre-operative serum creatinine level, decreased post-operative cardiac output, and high inotropic requirement (19–21, 24–28). Several studies have found out that there is a potential direct association between prolonged CPB times and the development of AKI. In a prospective pediatric multicenter study, the risk of developing AKI was 51 and 70% for bypass duration of more than 120 and 180 min, respectively (19). In a meta-analysis of nine studies, the authors concluded that longer CPB times are strongly associated with a higher incidence of AKI (29). Despite the consensus of the plausibility of the association between AKI and CBP duration, it is worth mentioning that this association was not observed in other studies. Some other technical and medical factors such as the flow rates, temperature, patient's hematocrit, and cardiac index probably play more interactive roles in determining the risk of AKI rather than the CBP time itself (30–32).

Development of AKI in post-cardiac surgery has been reported to be independently associated with increased morbidity and mortality in children, hospital length of stay, prolonged mechanical ventilation duration, more inotropic requirement, and increased mortality rate (17, 19, 20, 33).

Impact of AKI on Children Receiving ECMO

The Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) study is probably the most comprehensive study devoted to evaluating AKI and kidney supportive measures for critically ill children receiving ECMO (34). The study group utilized data of more than 800 pediatric ECMO patients from multiple centers to describe the incidence and timing of AKI by utilizing serum creatinine KDIGO criteria and to investigate the association of AKI with the length of ECMO need and mortality (35). The reported incidence of any stage AKI was 60%. Duration of ECMO support days and the need for renal replacement therapy were significantly higher in patients with AKI. The presence of AKI was associated with reduced survival to hospital discharge after controlling for multiple patients' characteristics and interventional support variables. In a separate analysis by the same group (36), the authors evaluated fluid overload as a modifiable risk of survival in critically ill children receiving ECMO. The median peak fluid overload was lower in patients who survived ECMO (27.2 vs. 44.4%) and those who survived until hospital discharge (24.8 vs. 43.3%).

Impact of AKI on Pediatric Patients With Severe Sepsis

Sepsis is common in pediatric patients admitted to the pediatric intensive care unit. Severe sepsis occurs in around 8% of pediatric ICU patients (37).

Sepsis and shock were reported as the most frequent risk factors for AKI in critically ill children. A nationwide Taiwanese study that included more than 60,000 critically ill children found that 46.5% of the AKI cases were due to sepsis (38). A similar finding was reported in a study by Fitzgerald et al. in which AKI occurred in 42% of severe pediatric sepsis patients and severe AKI occurred in about 20% (8, 39).

The etiology of AKI in patients with severe sepsis seems to be multifactorial. This includes poor kidney perfusion secondary to septic shock, inflammatory mediators, kidney vasculature micro-thrombosis, kidney parenchymal ischemia and necrosis, and the use of nephrotoxic medications. In patients with warm shock, there is a decrease in the vascular resistance, with higher kidney perfusion, but lower GFR (glomerular filtration rate) secondary to changes in kidney microcirculation.

Fitzgerald et al. conducted one of the most important works regarding the impact of AKI on critically ill children. The authors did a *post hoc* analysis of the sepsis prevalence, outcomes, and therapies (SPROUT) study, which enrolled about 7,000 pediatric patients with severe sepsis from 128 pediatric intensive care units from over 26 countries (37). Twenty-one percent of critically ill children with severe sepsis, according to the 2005 international pediatric sepsis consensus criteria, developed stage II or III AKI. AKI carried an adjusted OR risk of 2.5 to have a composite outcome of death or new disability (39).

Impact of AKI on Neonates

Premature and full-term neonates are unique in many health aspects. They are affected by the intrauterine environment, the stressful transition during delivery, and the postnatal complications.

AKI in neonates is multifactorial. Many risk factors were identified to complicate the ICU course of neonates. These risk factors can occur perinatally with early development of AKI or later during ICU admission. These risk factors include but are not limited to (1) prematurity, which is associated with incomplete nephrogenesis; (2) perinatal asphyxia and reperfusion injury following hypoxia (40, 41); and (3) the patency of the patent ductus arteriosus (PDA), which is associated with lower systemic vascular resistance and decreased kidney perfusion along with the use of NSAIDs to manage PDA (42). Other risk factors include low birth weight, congenital diaphragmatic hernia, bronchopulmonary dysplasia, and maternal nephrotoxic medications exposure like Angiotensin-Converting Enzyme (ACE) inhibitors (17). Other factors are associated with the late incidence of AKI such as sepsis, necrotizing enterocolitis with more than 50% of neonates with necrotizing colitis develop AKI (43), and the use of nephrotoxic medications in neonates like vancomycin, gentamicin, piperacillin-tazobactam, and amphotericin B. Some studies showed that more than 80% of premature babies receive at least one nephrotoxic medication (44, 45).

The prime attention of neonatal AKI was mainly highlighted in the last decade (46). The poor performance of serum creatinine and its fluctuated levels depending on the gestational and birth ages, especially in the first week of life in term babies and for a more extended period in premature babies, limited neonatal AKI research.

Several small, single-center studies in neonates with various primary morbidities such as congenital heart disease, hypoxic-ischemic injury, and very low birth weight infants suggest that AKI is common and that those with AKI have poor outcomes. A thorough AKI-core data were presented by the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study (47). AWAKEN is a comprehensive epidemiological study that was conducted to evaluate the impact of AKI in critically ill neonates. It included more than 2000 neonates admitted to 24 neonatal ICUs from Australia, Canada, India, and the United States. The study excluded infants admitted to NICU at 2 weeks of age or older, infants who underwent cardiovascular surgery repair of congenital heart disease within a week of life, infants diagnosed with lethal anomaly upon admission, and infants who died within 48 h of admission. The authors utilized the KDIGO definition of AKI with minor modifications to make the criteria applicable to neonates. The study showed that the overall incidence of AKI by meeting urine output or serum creatinine criteria was 29.9%. Neonates with gestational age < 29 weeks had the highest incidence rate of AKI (47.9%) (48). Infants who met the criteria for any stage AKI had a mortality rate of 9.7% compared to 1.4% without AKI. Within the AKI group, stage 3 AKI had higher mortality rates than stage 2 or stage 1. The impact of AKI on mortality was still significant after adjusting for multiple demographic characteristics, interventions, and comorbidities. Like other pediatric and adult literature, the authors reported longer hospital stay in neonates with AKI.

Impact of AKI on Patients Post-stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is the transplantation of multipotent stem cells taken from bone marrow, umbilical cord, or peripheral blood to treat various diseases (e.g., leukemias, immunodeficiencies, and inborn errors of metabolism). HSCT is associated with numerous acute and long-term complications. The pre-HSCT conditioning, its intensity, preexisting comorbidities, chemotherapy exposure, the stem cell source, immunosuppression, and post-HSCT complications all make this population a unique population of critically ill children frequently admitted to pediatric ICUs. AKI is a well-known and common complication of HSCT in children. One of the first pediatric epidemiological studies of AKI in HSCT recipients using pRILFE criteria to define AKI was conducted in 2016 by Kizilbash et al. (49). They reported that 84% of patients developed AKI within 100 days post-HSCT, making AKI a prevalent HSCT complication. Previous pediatric studies have reported AKI in 21–42% of recipients within the first 100 days post-stem cell transplant; this wide range of incidence can be attributed to the difference in the AKI definitions used in different studies (50–52). In 2015, a systematic review study that included five observational studies showed that one-third of children post-HSCT developed AKI, with a median onset time of 4–6 weeks after transplantation (53).

There is a wide range of reported mortality rates in children with AKI post-HSCT. A published paper in 2003 about kidney function in children post-HSCT (54) showed that the mortality rate in the first 30 days post-HSCT was 19%, and the mortality rate in the patients who had AKI, defined as doubling in serum creatinine, was 55%. Lane et al. reported a mortality rate of 77% in children who developed severe AKI requiring dialysis after HSCT (55). In the systematic review study referenced earlier, the overall 100-day mortality for pediatric patients with AKI post-HSCT patients ranged from 10.5 to 12% (53). Kizilbash et al. (49) showed that the overall survival rate in pediatric patients post-HSCT was significantly lower among patients with AKI than patients without AKI (75 vs. 94%), and severe AKI was independently associated with increased mortality. There was a significant incremental increase in the mortality rate with increased AKI severity. Other studies showed that 5–10% of pediatric patients with severe AKI post-HSCT required RRT (50, 51, 54, 56), and the survival rate among them was only 42% (57).

Many risk factors for AKI have been reported in the literature, and these include unrelated donor, severe graft vs. host disease, severe infections, sepsis, veno-occlusive disease, the use of nephrotoxic medications (cyclosporine, amphotericin B, foscarnet, methotrexate, and calcineurin inhibitors), anemia, and total body irradiation (51, 52, 56, 58–60).

Post-HSCT AKI is associated with long-term complications. Kizilbash et al. (49) reported that 8% of children who developed AKI post HSCT and were alive at 1 year developed CKD. Other studies have reported CKD in 10% of children at 1-year post-HSCT (50–52, 56).

THE IMPACT OF VOLUME OVERLOAD ON PEDIATRIC ICU PATIENTS

Multiple factors make critically ill children vulnerable to volume overload. The systemic inflammation, capillary leak, and the arbitrary use of intravenous fluids to manage hypotension are among many factors that can contribute to volume overload. Regardless of meeting the AKI definition, the concept of volume overload has received extensive attention in the recent pediatric AKI and critical care literature. Despite the lack of a clear definition of volume overload and utilization of different formulas to identify it, multiple pediatric studies (61–64) found a good correlation between the percentile ratio of positive balance from ICU admission to weight upon admission (percent volume overload) and mortality rate. The percent volume overload can be calculated using different formulas. The following formula is one of the most commonly used formulas to calculate the percent volume overload:

[(total fluid intake (L) - total fluid output in liters (L))/(admission weight in kilograms) $*$ 100] (64, 65).

By utilizing the above formula, Gillespie et al. (62) reported a death odds ratio (OR) of 3.02 for patients with >10% volume overload. Foland et al. (63) reported a death OR of 1.8 for each 10% volume overload increase and Hayes et al. reported an OR of 6.1 for volume overload of >20%.

However, such association between volume overload and mortality was not duplicated by Diaz et al. (66), who concluded that despite being common in children, volume overload in critically ill children was not an independent mortality risk factor after adjusting for other covariates. It is worth mentioning that AKI was an independent mortality risk factor in that study.

Selewski et al. evaluated the impact of volume overload in a specific ICU population. The group published a comprehensive 5-year multicenter evaluation of fluid overload and its association with patients' outcomes in children managed by ECMO (36). They found that fluid overload is common in children receiving ECMO, as more than 50% of patients had more than 10% fluid overload, and it was associated with prolonged ECMO duration and increased mortality independently when adjusted for other factors, including AKI.

Similarly, in patients with severe sepsis, Wong et al. found that cumulative fluid overload percent in the first 5 days of ICU admission was consistently and independently associated with increased mortality, fewer ventilator-free days, more inotrope utilization, and increased length of stay (67).

Two *post hoc* analyses from the AWAKEN study group evaluated the impact of volume overload in term and premature critically ill neonates (68, 69). The authors evaluated the percentile by calculating fluid balance during the first week of life using the formula: (daily weight – birth weight)/(birth weight $\times$ 100). The primary outcome was set for the need for mechanical ventilation on day 7 of life. The authors found that high positive fluid balance during the first week of life is independently associated with the primary outcome. However, the multivariate analysis did not show a solid association between positive volume balance and survival. The authors commented that the lack of statistical signal can be contributed to the low incidence of mortality in both cohorts of neonates.

A collective conclusion of the significance of volume overload in critically ill children regardless of the underlying etiology was highlighted in a systematic review and meta-analysis published in 2018 (70). In this work, the authors looked into more than 40, mainly retrospective studies, and found that the volume overload was associated with a 6% increase in adjusted risk of mortality. The study shed light on a major inconsistency among different studies in calculating and defining volume overload and its severity. Despite this, the authors concluded that their findings were robust and consistent in suggesting that fluid overload carried a greater risk for mortality and prolonged ventilator utilization.

Volume overload is common in critically ill children after cardiopulmonary resuscitation. Fluid resuscitation is a fundamental component of the metabolic phase of the three-phase pathophysiology model of cardiac arrest (71), and large volumes of intravenous fluids are often administered to increase the cardiac output and global oxygen delivery during this phase. However, the clinical course of these patients is commonly complicated with oliguric AKI and poor diuresis of the administered fluids. With the growing evidence of the deleterious impact of volume overload, conservative fluid management was proposed to decrease the risk of volume overload after resuscitation. A meta-analysis that included 49 studies concluded that conservative fluid strategy results in an increased number of ventilator-free days and a decreased length of ICU stay compared with a liberal strategy or standard care without observing a difference in mortality rates (72). Thus, when prescribing fluids during or after resuscitation, fluids should be used wisely. The conceptual model of "Four Phases of Intravenous Fluid Therapy" provides a pathophysiologic approach in managing the fluids around resuscitation time. These phases are rescue, optimization, stabilization, and de-escalation. More details about this model can be obtained from (73, 74).

AKI AND COVID-19 CRITICALLY ILL CHILDREN

According to the World Health Organization (WHO), since being declared as a global pandemic in March 2020 by the WHO, coronavirus disease 2019 (COVID-19) cases reached more than 115 million globally by the end of February 2021 as per the WHO COVID-19 dashboard. Pediatric COVID-19 cases account for around 1% of total COVID-19 cases reported by the Chinese center for disease control and prevention. Most children with COVID-19 had mild illnesses than adults, and only 0.6% of infected children have severe symptoms (75), with infants being affected more with severe illness (76, 77). While the early data

in adults suggested that AKI was related to increased mortality risk, even after adjustment for age, sex, and comorbidities (78), the early data in children were not precise and probably conflicting. For example, one of the first studies describing AKI in COVID-19 children was published by Wang et al. (79), who reviewed 238 pediatric patients with confirmed COVID-19 from Wuhan Children's hospital; only three patients were sick and required ICU admission, and they developed AKI (incidence rate of 1.2%). The AKI in the three patients was part of the multisystem inflammatory syndrome and required supportive care with renal replacement therapy and plasma exchange. However, the data from Great Ormond Street Hospital in London (80) suggested a higher incidence of AKI than the Chinese study. AKI incidence was reported in 29% of 52 children with COVID-19 infection in the British report. AKI was again part of a multisystem inflammatory syndrome in most of the cases. None of the AKI cases required support with renal replacement therapy. To overcome this discrepancy, a multicenter cross-sectional study in SARS-CoV-2-infected critically ill children from six countries, but mainly from US centers, was conducted to evaluate the epidemiologic aspect of AKI in this cohort (81). The preliminary results of this study showed that among the 41 participating centers, only 26 centers reported COVID-19 children required ICU admission during the study period. Almost half (44%) of the enrolled critically ill children (a total of 106) developed AKI by KDIGO serum creatinine criteria. Despite the high prevalence, the AKI severity was not momentous as none of these patients needed dialysis despite the relatively high mortality rate among this cohort (6%). Diagnosis of shock and inotropic requirement at the time of admission were the main risk factors for AKI in univariate analysis. The authors concluded that the high prevalence of AKI in critically ill children would add more complexity to these children's medical care and recommended early identification of AKI to adjust the management accordingly.

CONCLUSION

In this review, we depicted the impact of AKI in critically ill children in pediatric ICUs. The most recent literature consensus supports the conclusion that AKI is common in pediatric ICUs in general and in specific cohorts of critically ill children. AKI and its sequelae, such as volume overload, are considered consistent and independent risk factors for different outcomes such as mortality rates and ICU length of stay.

AUTHOR CONTRIBUTIONS

BL did the literature review and wrote the first draft. AK did literature review and finalized the submitted version of the manuscript. All authors contributed to the article and approved the submitted version.

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Continuous Renal Replacement Therapy in Critically Ill Children in the Pediatric Intensive Care Unit: A Retrospective Analysis of Real-Life Prescriptions, Complications, and Outcomes

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Introduction: Severe acute kidney injury is a common finding in the Pediatric Intensive Care Unit (PICU), however, Continuous Renal Replacement Therapy (CRRT) is rarely applied in this setting. This study aims to describe our experience in the rate of application of CRRT, patients' clinical characteristics at admission and CRRT initiation, CRRT prescription, predictors of circuit clotting, short- and long-term outcomes.

Methods: A 6-year single center retrospective study in a tertiary PICU.

Results: Twenty-eight critically ill patients aged 0 to 18 years received CRRT between January 2012 and December 2017 (1.4% of all patients admitted to PICU). Complete clinical and CRRT technical information were available for 23/28 patients for a total of 101 CRRT sessions. CRRT was started, on average, 40 h (20–160) after PICU admission, mostly because of fluid overload. Continuous veno-venous hemodiafiltration and systemic heparinization were applied in 83.2 and 71.3% of sessions, respectively. Fifty-nine sessions (58.4%) were complicated by circuit clotting. At multivariate Cox-regression analysis, vascular access caliber larger than 8 Fr [HR 0.37 (0.19–0.72), $p = 0.004$] and regional citrate anticoagulation strategy [HR 0.14 (0.03–0.60), $p = 0.008$] were independent protective factors for clotting. PICU mortality rate was 42.8%, and six survivors developed chronic kidney disease (CKD), within an average follow up of 3.5 years.

Conclusions: CRRT is uncommonly applied in our PICU, mostly within 2 days after admission and because of fluid overload. Larger vascular access and citrate anticoagulation are independent protective factors for circuit clotting. Patients' PICU mortality rate is high and survival often complicated by CKD development.

Keywords: acute kidney injury, hemodialysis, artificial membranes, blood clotting, vascular catheters, chronic kidney disease

INTRODUCTION

Acute kidney injury (AKI) is a common complication in the Pediatric Intensive Care Unit (PICU), involving approximately one third of critically ill neonates and children (1, 2). Although Continuous Renal Replacement Therapy (CRRT) is usually applied in critically ill adult patients with severe AKI and/or multiple organ dysfunction syndrome (MODS) in order to support kidney function (3–5), this technique is uncommonly used in the PICU (6). In a large multicenter observational study, only 1.5% of critically ill children underwent CRRT (2). A knowledge gap exists regarding clinical and technical peculiarities of CRRT in the pediatric population (7), and several researchers in the field encourage the sharing of experiences and clinical and technical data (8–11). Predictors for circuit clotting are mostly unknown and originate from large cohorts of adult patients (12, 13). Uncertainties also exist on long-term kidney and global outcomes of critically ill pediatric patients who underwent CRRT. Although CRRT has been recognized as a strong predictor of short-term mortality, particularly when associated with fluid overload (FO) and MODS (14–17), pediatric AKI patients undergoing CRRT often encounter delays in referral to the nephrology unit or are lost to long-term follow-up (10, 18).

In this single center retrospective study we observe a cohort of pediatric critically ill patients with the aim of describing: (1) the rate of application of CRRT; (2) the demographic and clinical characteristics at PICU admission of patients treated with CRRT; (3) timing-to-start, indication, and technical prescription for CRRT; (4) baseline predictors (at CRRT initiation) of premature circuit clotting; (5) short- and long-term outcomes of CRRT patients, both in terms of PICU survival and nephrology follow-up.

MATERIALS AND METHODS

Data Collection and Definitions

In this single center, retrospective, observational study, we included all consecutive patients aged 0 to 18 years who received CRRT during their PICU stay at the Meyer Children's Hospital (Florence, IT) from January 2012 to December 2017. Rate of CRRT application, along with patients' clinical data at PICU admission [i.e., anthropometric and clinical characteristics, such as admission diagnosis, urinary output (UO), accumulated FO, need for vasopressors or mechanical ventilation] are described. In the subgroup of patients where data on CRRT prescription and delivery were available, we also described patients' clinical characteristics at CRRT initiation and CRRT technical features. In particular, UO, FO, and laboratory data were collected immediately before CRRT initiation, along with timing-to-start and indication for CRRT. Being a retrospective observational study, CRRT initiation was determined by the attending physicians according to local policy and practice. Technical data include information on CRRT initial prescription (i.e., treatment modality, filter type, treatment duration, adopted vascular access, anticoagulation strategy), and minute-by-minute treatment delivery information recorded on the CRRT monitor memory card (e.g., flows, pressures, and machine alarms). Combined analysis of overtime pressure drop and overtime transmembrane pressure (TMP) and machine alarms allowed the identification of unintended discontinuation sessions due to membrane fouling. Stopped sessions were reported as "clotted" if pressure drop had increased above 150 mmHg and/or clotting machine alarms had been identified in the machine recorded treatment data. Technical CRRT data regarding CRRT prescription, available for each delivered session, were used to identify predictors for circuit clotting. Recorded treatment data were analyzed to identify treatment clogging (TMP elevation >250 mmHg) and vascular access dysfunction (negative access pressure, below −100 mmHg for a cumulative time longer than 120 min). Patients experiencing a rate of clotted sessions >25% of total CRRT sessions were considered as patients with "high clotting rate." On this basis, patients' clinical and laboratory characteristics were also reported according to clotting rate.

Finally, mortality rate at PICU discharge, long-term patient survival, proteinuria or chronic kidney disease (CKD) development at last available follow-up, and referral to nephrology outpatient clinic were evaluated. Patients were considered lost to follow-up if data in the hospital electronic chart were not available. Three authors (EB, BT, and FG) independently performed data extraction and collection and subsequently cross-checked the results. Discrepancies were re-examined by GV. AKI was defined according to KDIGO criteria (19), while percentage of FO was defined as *[(fluid in – fluid out)/PICU admission weight]*100*, as previously described (20). Proteinuria and CKD were defined based on KDIGO definitions (urinary albumin-to-creatinine ratio >3 mg/mmol; eGFR < 90 ml/min/1.73 m^2, bed-side Schwartz formula), while end stage kidney disease (ESKD) was defined by initiation of chronic replacement therapy (intermittent hemodialysis or kidney transplantation) (21). Patients' clinical and laboratory characteristics were also reported according to PICU survival.

Statistical Analysis

Descriptive statistics were reported as appropriate after testing continuous variables for normality of the distribution by the Shapiro-Wilk test. Frequency and percentage were reported for qualitative variables, while mean and standard deviation were calculated for quantitative variables. Median and interquartile range (IQR) were calculated for quantitative variables with non-normal distribution. Kaplan-Meier survival analysis was run to evaluate parameters associated with premature clotting. Univariate logistic regression and Cox regression analysis were performed to estimate the size of association between clinical and technical variables and patient's clotting rate, circuit premature clotting, and PICU survival. Odds ratio (OR), hazard ratio (HR) and their 95% confidence interval (95%CI) were reported. For circuit clotting prediction, variables with a Wald test's p-value <0.10 in the univariate analysis were considered for multivariate Cox regression analysis. Independent predictors for premature clotting were identified through backward selection based on the AIC. Statistical significance was set to p-value < 0.05. Statistical analysis was performed using R© software version 3.5.1.

TABLE 1 | Demographic and clinical characteristics at pediatric intensive care unit admission.

ID	Sex, age	Height (cm), Weight (Kg)	BSA (m^2)	Admission diagnosis	UO (ml/Kg/h), FO (%)	VP—MV
1	M, 1d	56, 3	0.21	Meconium aspiration	4.0, 22.0	1–1
2	M, 8d	60, 3	0.22	Pulmonary HTN	2.7, 0.5	1–1
3	M, 2m	52, 4	0.23	TAPVR	2.5, −0.5	1–1
4	M, 2m	60, 6.6	0.31	Septic shock	0.0, 0.0	1–1
5	M, 5m	62, 6	0.31	Tracheomalacia	4.2, 1.7	0–0
6	M, 11m	75, 9	0.42	HUS	0.4, 8.0	0–1
7	M, 1y	52, 2	0.17	Pneumonia	8.6, 1.5	1–1
8	F, 1y	75, 10	0.44	Severe AKI	0.1, 3.9	0–1
9	M, 1y	82, 10	0.47	T cell leukemia	0.3, 7.5	1–1
10	F, 1y	82, 12	0.50	HUS	0.7, 5.7	0–1
11	F, 2y	81, 12	0.50	Pneumonia	3.8, 6.2	1–1
12	F, 2y	90, 12	0.54	Pneumonia	0.4, 10.4	0–0
13	F, 2y	100, 12	0.58	Septic shock	8.2, 3.1	0–1
14	F, 2 y	91, 14	0.58	MAS	0.6, 4.0	1–1
15	M, 2y	92, 14	0.59	T cell leukemia	3.4, 2.8	0–1
16	M, 4y	90, 13	0.56	Pneumonia	3.3, 4.2	0–1
17	F, 4y	92, 16	0.62	Severe AKI	3.7, −2.7	0–1
18	M, 4y	98, 14	0.61	X-CGD	5.9, 1.1	1–1
19	F, 5y	96, 13	0.58	Pulmonary edema	0.7, 3.5	0–1
20	F, 5y	86, 17	0.61	FB ingestion	0.0, 3.3	1–1
21	F, 5y	105, 25	0.82	Pneumonia	0.2, 0.7	0–1
22	F, 9y	120, 29	0.97	B cell leukemia	1.5, 0.9	1–0
23	F, 10y	160, 75	1.78	Rhabdomyolysis	6.5, −1.5	1–1
24	F, 11y	125, 20	0.85	Septic shock	0.0, 5.4	1–1
25	M, 12y	130, 26	0.98	Septic shock	0.2, −2.8	0–1
26	M, 15y	163, 68	1.73	B cell leukemia	1.1, 0.1	0–1
27	F, 16y	165, 52	1.56	ALL	3.5, 3.7	1–1
28	F, 17y	168, 50	1.56	Septic shock	5.5, 7.3	0–0

Age (d, days; m, months; y, years); AKI, acute kidney injury; ALL, acute lymphoblastic leukemia; BSA, body surface area; FB, foreign body; FO, fluid overload; HTN, hypertension; HUS, hemolytic uremic syndrome; MAS, macrophage activation syndrome; MV, need for mechanical ventilation; PICU, pediatric intensive care unit; Sex (F, female; M, male); TAPVR, total anomalous pulmonary venous return; UO, urinary output; VP, need for vasopressors; X-CGD, x-linked chronic granulomatous disease; 0 = no; 1 = yes.

Ethical Concerns

The present study has been approved by the Meyer Children's Hospital Ethics Committee (registry number 104/2020). Being an observational study, the Ethics Committee waived informed consent for the analysis. Patients enrolled in this study did not receive additional medical, pharmacological or behavioral interventions other than those routinely administered in the PICU. Research was carried out in agreement with the principles of the original Declaration of Helsinki and its later amendments.

RESULTS

Rate of CRRT Application and Patients' Characteristics at PICU Admission

Of the 1,996 patients admitted to the Meyer Children's Hospital PICU in the 6-year study period, 28 patients (1.4%) received CRRT (**Table 1**). In this cohort of CRRT patients, median age at PICU admission was 2 years [1–6], with a slightly higher proportion of females (15/28, 53.6%). Median height, weight, and body surface area were 90 cm [75–108], 13.0 Kg [9.8–21.3], and 0.58 m^2 [0.45–0.84], respectively. PICU admission diagnoses were: respiratory failure, pneumonia or respiratory distress (10/28, 35.7%), septic shock (5/28, 17.9%), onco-hematological disease (5/28, 17.9%), hemolytic uremic syndrome, severe AKI or rhabdomyolysis (5/28, 17.9%), and others (3/28, 10.7%, macrophage activation syndrome $n = 1$, pulmonary hypertension $n = 1$, X-linked chronic granulomatosis $n = 1$) (**Table 1**). At PICU admission, median urinary output and fluid overload were 2.00 ml/Kg/h [0.36–3.82] and 3.2% [0.6–5.5], respectively, while mechanical ventilation was needed in 24/28 (85.7%) patients. Hemodynamic instability requiring vasopressors was observed in 14/28 (50%) cases at PICU admission (**Table 1**).

TABLE 2 | Clinical and biochemical characteristics at continuous renal replacement therapy initiation; number, duration, and clotting rate.

ID	Time-to-start (h)	Indication	UO (ml/Kg/h), FO (%)	sCr (umol/L)	BUN (mmol/L)	K (mmol/L)	CRRT sessions	
							Number, mean duration (h)	Clotting rate
1	17	FO	1.8, 24.1	92.8	3.2	5.9	10, 27.5	2/10
2	150	FO	1.1, 31.1	61.9	22.8	3.5	3, 21.1	3/3
5	217	FO	1.3, 120.7	35.4	6.0	3.8	5, 29.3	3/5
6	7	Hyperazotemia	0.1, 0.4	594.2	51.2	4.8	5, 38.4	1/5
7	395	FO	4.0, 200.0	77.8	37.3	6.6	4, 12.3	1/4
8	4	Hyperazotemia	0.0, 1.8	634.0	58.2	6.5	9, 20.1	8/9
9	41	FO	0.5, 27.4	114.9	29.3	4.7	4, 16.4	4/4
10	60	FO	0.2, 21.1	201.6	20.3	3.4	2, 21.5	2/2
11	74	FO	5.1, 12.4	62.8	13.0	3.5	1, 22.2	1/1
12	18	FO	0.5, 15.1	142.4	19.5	3.6	5, 49.7	4/5
13	27	FO	2.1, 10.4	114.9	21.7	4.3	7, 10.0	6/7
14	28	FO	1.5, 8.2	22.1	8.0	5.1	3, 48.9	0/3
15	168	FO	2.1, 18.5	82.2	22.5	4.6	6, 66.5	2/6
16	219	Hyperkalemia	0.3,−4.1	133.5	37.3	6.0	7, 74.9	0/7
18	40	FO	1.8, 10.8	79.6	7.3	3.4	4, 59.7	2/4
19	11	Hyperazotemia	0.4, 4.7	847.1	44.3	4.1	1, 9.8	0/1
20	22	Hyperkalemia	0.0, 2.8	132.6	6.0	5.9	1, 4.5	1/1
21	7	Hyperazotemia	0.1, 0.7	610.1	48.3	4.5	3, 68.8	0/3
22	188	FO	0.1, 8.9	70.7	6.7	3.3	1, 32.1	1/1
23	61	Hyperazotemia	0.8, 4.9	448.3	29.3	4.8	8, 49.5	7/8
25	29	Shock in IHD	1.9, 0.1	IHD	20.3	5.4	6, 31.0	3/6
26	38	Hyperazotemia	0.7,−0.2	154.7	44.8	4.4	4, 64.2	2/4
28	210	FO	2.7, 28.6	238.7	24.5	4.5	2, 79.8	0/2

Clotting rate represents the proportion of clotted sessions for each patient. A clotting rate > than 25% identifies patients at "high clotting rate." BUN, blood urea nitrogen; FO, fluid overload; IHD, intermittent hemodialysis; K, potassium; sCr, serum creatinine; Time-to-start, time from admission to CRRT initiation; UO, urinary output.

CRRT Indication and Prescription

Clinical characteristics of 23 patients are described in **Table 2**. All of the 23 patients were treated with Prismaflex® (Baxter, Deerfield, Illinois) machine, for a total of 101 treatment sessions.

Median time from PICU admission to CRRT initiation was 40 h [20–160], and indications for CRRT initiation were fluid overload in 14/23 (60.9%) patients, hyperazotemia and/or hyperkalemia in 8/23 (34.8%) patients. At CRRT initiation, median UO, FO, serum creatinine, blood urea nitrogen, and potassium were 0.75 ml/Kg/h [0.27–1.89], 10.4% [2.3–22.6], 124 umol/L [78–229] (1.4 mg/dl [0.9–2.6]), 22.5 mmol/L [10.5–37.3] (63 mg/dl [29–105]), and 4.5 mmol/L [3.7–5.3], respectively (**Table 2**). Median hemoglobin, hematocrit, and calcium levels were 6.2 mmol/L [5.3–7.1], 28.9% [25.7–34.6], and 2.26 mmol/L [1.96–2.44], respectively. **Table 2** also shows the number of CRRT sessions for each treatment, as well as mean session duration, and proportion of clotted sessions for each patient. Clotting rate was higher than 25% in 15 patients (65.2%).

Among the 101 CRRT sessions, the most common prescription was Continuous Veno-Venous Hemodiafiltration (CVVHDF) (84/101, 83.2%), and 3/4 treatments were performed with a AN69ST membrane (acrylonitrile and sodium methallyl sulfonate copolymer) (**Table 3**). Filters with surface area smaller than 0.6 m^2 were used in 13.8% of sessions. The most frequently used access site was the femoral vein, and 17 sessions were linked to an ECMO circuit (patient IDs 1, 2, 11, 18). Median access length and caliber were 12 cm and 8.0 Fr, respectively. In all patients, packed red blood cells were used to prime the extracorporeal circuit. The most common anticoagulation method was continuous systemic unfractioned heparin (72/101, 71.3%) with an average dose of 13.9 U/Kg/h, while regional citrate anticoagulation (RCA) was used in 11/101 (10.9%) sessions. Eighteen sessions (17.8%) were performed with no anticoagulation for clinical decision. CRRT was continued for a median of 12 days [7.75–17] and sessions lasted for a median of 30.2 h [7.1–65.6].

Predictors of Unintended Discontinuation Due to Clotting

Unintended treatment discontinuation due to clotting was detected in more than half of CRRT sessions (59/101, 58.4%), after a median session duration of 21.2 h [7.1–42.1]. Every clotted session showed an increase in TMP (indicating membrane

TABLE 3 | Prescription characteristics and clotting predictors of continuous renal replacement therapy sessions.

Parameter	Total ($n = 101$)	No clotting ($n = 42$)	Clotting ($n = 59$)	HR [95% CI]	*P*
Treatment modality					0.059
CVVHD	16 (15.8%)	3 (18.8%)	13 (81.2%)	Ref.	
CVVHDF	84 (83.2%)	39 (47.0%)	45 (53.0%)	0.50 [0.27–0.94]	**0.031**
SCUF	1 (1.0%)	0 (0.0%)	1 (100.0%)	1.64 [0.21–12.76]	0.635
Filter type					**0.033**
HF1000	4 (4.0%)	0 (0.0%)	4 (100.0%)	Ref.	
HF20	14 (13.9%)	4 (28.6%)	10 (71.4%)	1.47 [0.46–4.71]	0.520
M60	16 (15.8%)	8 (50.0%)	8 (50.0%)	0.53 [0.16–1.78]	0.304
ST60	39 (38.6%)	16 (41.0%)	23 (59.0%)	0.65 [0.22–1.91]	0.437
ST100	15 (14.9%)	10 (66.7%)	5 (33.3%)	0.28 [0.07–1.07]	0.063
ST150	6 (5.9%)	3 (50.0%)	3 (50.0%)	0.35 [0.07–1.56]	0.168
SEPTEX	7 (6.9%)	1 (14.3%)	6 (85.7%)	1.26 [0.36–4.49]	0.718
Membrane type					**0.005**
PAES	18 (17.8%)	4 (22.2%)	14 (77.8%)	Ref.	
AN69ST	76 (75.2%)	37 (48.7%)	39 (51.3%)	0.39 [0.21–0.74]	**0.004**
PAES-HCO	7 (6.9%)	1 (14.3%)	6 (85.7%)	0.98 [0.38–2.56]	0.969
Filter area					**0.030**
0.2 m^2	14 (13.8%)	4 (28.6%)	10 (71.4%)	Ref.	
0.6 m^2	55 (54.5%)	24 (43.6%)	31 (56.4%)	0.43 [0.21–0.88]	**0.022**
$\geq$ 1 m^2	32 (31.7%)	14 (43.6%)	18 (56.4%)	0.36 [0.16–0.79]	**0.010**
Prescription flows					
Blood flow (ml/min)	60 [40–80]	60 [50–100]	60 [40–80]	0.99 [0.99–1.00]	0.379
Dialysate flow (ml/h)	400 [200–600]	400 [250–500]	400 [100–800]	1.00 [1.00–1.00]	0.073
Replacement flow (ml/h)	200 [50–400]	200 [50–500]	200 [0–400]	0.99 [0.99–1.00]	0.309
Net ultrafiltration (ml /h)	40 [25–70]	40 [25–60]	40 [25–70]	1.00 [0.99–1.00]	0.726
Effluent flow (ml /h)	900 [510–1120]	790 [525–1080]	910 [390–1130]	1.00 [0.99–1.00]	0.739
Filtration fraction (%)	17.1 [9.1–23.8]	15.6 [5.7–22.4]	18.7 [11.3–23.9]	1.00 [0.98–1.03]	0.849
Vascular access site					0.175
Jugular	29 (28.7%)	18 (62.1%)	11 (37.9%)	Ref.	
Femoral	55 (54.5%)	20 (36.4%)	35 (63.6%)	1.51 [0.76–2.97]	0.238
ECMO	17 (16.8%)	4 (23.5%)	13 (76.5%)	2.16 [0.96–4.82]	0.062
Vascular access caliber	8.0 [8.0–8.5]				**0.004**
$\leq$ 8 Fr	65/92 (70.7%)	24 (36.9%)	41 (63.1%)	Ref.	
> 8 Fr	27/92 (29.3%)	16 (59.3%)	11 (40.7%)	0.37 [0.19–0.72]	
Vascular access length	12.0 [11.5–14.0]				0.806
$\leq$ 12 cm	46/71 (64.8%)	22 (47.8%)	24 (52.2%)	Ref.	
> 12 cm	25/71 (35.2%)	10 (40.0%)	15 (60.0%)	0.92 [0.48–1.76]	
Anticoagulation					**0.010**
None	18 (17.8%)	5 (27.8%)	13 (72.2%)	Ref.	
Heparin	72 (71.3%)	28 (39.4%)	44 (60.6%)	0.75 [0.40–1.40]	0.376
Citrate	11 (10.9%)	9 (81.8%)	2 (18.2%)	0.13 [0.03–0.59]	**0.008**

AN69ST, acrylonitrile and sodium methallyl sulfonate copolymer; CVVHD(F), continuous veno-venous hemodialysis (Hemodiafiltration); HCO, high cut-off; HR, hazard ratio; PAES, polyarylethersulfone; Ref., reference; SCUF, slow continuous ultrafiltration.

clogging in most of the cases), and 50/59 (84.7%) sessions also presented signs of vascular access dysfunction. Variables significantly associated with clotting in the univariate Cox regression analysis were membrane type ($p = 0.005$), filter area ($p = 0.03$), vascular access caliber ($p = 0.004$), and anticoagulation strategy ($p = 0.01$) (**Table 3**). In particular, most of the sessions performed with a polyarylethysulfone (PAES) high-flux membrane (77.8%), using a filter with smaller surface area (71.4%), via a smaller vascular access ($\leq$8 Fr, 63.1%), and without regional citrate anticoagulation (72.2 and 60.6%, respectively, for no-anticoagulation and systemic heparinization) underwent premature clotting. Initial prescription flows were not significantly different between clotting and no-clotting groups. Multivariate Cox regression analysis identified dimension (in

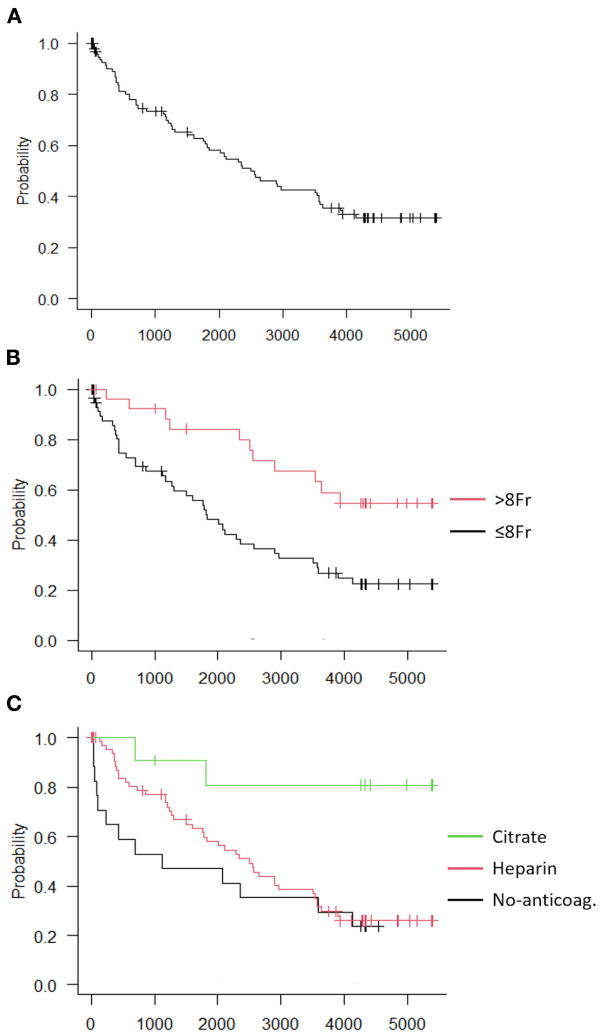

FIGURE 1 | Kaplan-Meier curves of session-related clotting independent risk factors. **(A)** Clotting-free survival analysis of all 101 sessions, **(B)** Sessions divided according to vascular access caliber, **(C)** Sessions divided according to anticoagulation method.

Fr) of the vascular access [HR 0.37 (0.19–0.72), $p = 0.004$] and RCA strategy [HR 0.14 (0.03–0.60), $p = 0.008$] as two baseline independent predictors for premature clotting (**Figure 1**). Among the 23 patients, 8 (34.8%) experienced clotting in ≤25% of CRRT sessions and were thus considered as patients with "low clotting rate." On the other hand, the remaining 15 (65.2%) patients had clotting in more than 25% of CRRT sessions and were thus considered as patients with "high clotting rate." Patients' clinical characteristics at CRRT initiation are described for both groups in **Supplementary Table 1**. No significant clinical predictors were found in these groups.

Short- and Long-Term Outcomes

Considering the whole study population ($n = 28$), average PICU length of stay was 24 days [12–30], with a PICU mortality rate of 42.8% (12/28). Baseline clinical and CRRT characteristics of patients who died and patients who survived to PICU discharge are described in **Supplementary Table 2**. Requirement of vasoactive treatment was the only predictor of mortality among these subgroups. Of the 16/28 CRRT patients successfully discharged from the PICU, one was a ESKD patient already treated with IHD before PICU admission; three were lost to follow-up soon after discharge; the remaining 12 had at least 1 year follow-up, with a mean follow-up length of 3.5 ± 2.0 years. Among these 12 patients, only 5 (42%) did not develop any form of kidney dysfunction, one (8%) developed low grade proteinuria, three (25%) developed CKD, and three (25%) developed ESKD (**Table 4**). Of note, 3/5 (60%) patients who did not develop kidney disease have a follow-up of only 1 year after discharge. Overall, 7/15 patients (46.7%) were never referred to nephrology follow-up after PICU discharge.

DISCUSSION

In this single center retrospective study, we have observed a rate of CRRT application of 1.4% in a cohort of pediatric critically ill patients admitted to a tertiary pediatric hospital. In our cohort, extracorporeal treatments were applied within 48 h after PICU admission and mainly for management of fluid overload. Most of the treatments were performed in CVVHDF modality, with large (>0.6 m^2) acrylonitrile high-flux membranes and systemic heparinization. Large vascular access (>8 Fr) and RCA were independent protective factors for circuit clotting. Patients' PICU mortality rate was high and survival often complicated by CKD development.

In the context of a general lack of clinical and technical information on CRRT in PICU, here we accurately describe our cohort of pediatric CRRT patients in terms of clinical presentation, treatment prescription, and CRRT indication. Our results are in agreement with the available literature. The findings confirm the relative low rate of application of CRRT in PICU and describe FO as the main indication for CRRT initiation (22). In the literature, the most frequent clinical indication for CRRT is severe AKI complicated with the concomitant the requirement of fluid administration (diuretic-unresponsive oligo-anuria and subsequent FO) and/or metabolic (untreatable acidosis, hyperkalemia, and uremic toxins accumulation) disturbances (23). However, no clear cut-off values for CRRT initiation are currently available and, as a consequence, timing is controversial, even in adult patients (24–29). Since almost two decades, FO has been identified as a main independent predictor of mortality in the PICU setting (14, 20). The US multicenter, prospective, pediatric CRRT (ppCRRT) registry has led to numerous studies addressing diverse clinical questions about CRRT patients and modalities (6). Evidence from these studies suggests that survival is greatly influenced by the underlying disease at admission. It also highlights the importance of circuit survival and nutritional prescription, and it confirms the independent association between FO at CRRT initiation and mortality (15, 30). However, these studies failed to define a target %FO for CRRT initiation or to determine if aggressive treatment of FO could improve survival in these

TABLE 4 | Long-term follow-up after pediatric intensive care unit survival.

ID	PICU stay (d)	PICU survival	Follow-up data	Follow-up time (y)	Kidney outcome
1	30	yes	yes	6.5	ok
6	22	yes	yes	3	proteinuria
8	27	yes	yes	6	ESKD
10	13	yes	yes	1	ok
11	25	yes	yes	1	ok
12	30	yes	yes	3.5	CKD
13	29	yes	no	-	-
14	25	yes	no	-	-
16	97	yes	yes	1	CKD
17	4	yes	yes	6	CKD
19	26	yes	yes	5	ESKD
21	40	yes	no	-	-
23	34	yes	yes	2.5	ok
24	51	yes	yes	6	ESKD
25	12	yes	IHD		
28	52	yes	yes	1	ok

CKD, chronic kidney disease; ESKD, end-stage kidney disease; IHD, intermittent hemodialysis; PICU, pediatric intensive care unit; Time (d, days; y, years).

patients (6). It has been suggested that CRRT should be started rapidly in oligo-anuric patients, before a FO threshold of 10–20% is reached (15). Retrospective cohort studies suggest that earlier CRRT initiation is associated with improved survival (31), with mortality increasing per each hour of delay (16), but other studies also stress that CRRT initiation confers a more than eight-fold higher mortality risk with respect to the total PICU population (17). In fact, CRRT patients, especially children, can experience complications related to vascular access placement, anticoagulation and blood loss, hypotension, and electrolytes derangement (32–34). Particularly in small pediatric patients, maintenance of filter patency and avoidance of premature clotting are crucial to increase safety, efficacy and effectiveness of the treatment (9). Beside undertreatment caused by membrane fouling and downtime due to circuit substitution (35), the amount of blood retained into the extracorporeal circuit for unexpected clotting can be clinically relevant in a small pediatric patient. Risk factors for filter clotting should be explored in pediatric population and clinical practice improved in order to minimize this harmful complication.

In line with previous experiences reported in the literature (36, 37), we found that dimension of vascular access and anticoagulation strategy were independent predictors for circuit clotting. In particular, smaller vascular access ($\leq$8 Fr) was significantly associated with filter clotting. This was likely associated with the fact that treatments in smaller patients, carrying the smallest catheters sizes were those complicated by more frequent unintended interruptions. Interestingly, overtime analysis of access pressure during treatment revealed signs of vascular access dysfunction in most of the clotted sessions. Thus, when possible, a larger catheter should always be used for vascular access. Unfortunately, use of large catheters is often not feasible in newborn or small pediatric patients. In these cases, the adoption of hardware components specifically designed for pediatric patients might help delivering an adequate CRRT session. It is also possible that the internal jugular vein might be preferred in order to optimize circuit patency (6). As described in our population, however, this access in critically ill children may frequently be already utilized for a central venous catheter and the only available option could be to select the femoral vein. Even if in our study access site did not show significant differences in terms of clotting rate, it might be interesting in larger studies to further address this important aspect. Again, regardless of vascular access site and size, miniaturized disposable, filters, and roller pumps, mainly, might reduce the amplitude of excessive cyclic pressure oscillations, led by large peristaltic pumps flowing fluids against small tubes and vascular accesses (38, 39). In this context, Carpediem® (Cardio Renal Pediatric Emergency Machine) (Bellco-Medtronic, Mirandola, Italy) might be proposed for smaller patients, especially those with "high clotting rate" characteristics. Interestingly, despite the relatively small size of patients enrolled in our cohort, filters with surface area smaller than 0.6 m^2 were used in <15% of sessions. Moreover, our results confirm RCA as a major independent protective factor to reduce circuit clotting, compared to heparin or no-anticoagulation strategies. Therefore, also according to the literature, RCA should be adopted as a first choice anticoagulation strategy for CRRT.

Mortality in our study was similar to that reported in the ppCRRT study (42%) (6) but higher than the results of the AWARE trial (25%) (2). The latter study involved 4,984 critically ill children and young adults and described RRT as one of the most important predictors of mortality in the PICU [OR 3.38 (1.74–6.54)] (2). Moreover, it is possible that the population described in our study was mainly composed by children with multiple organ failure, similarly to that reported in the pediatric registry (6). The availability of data on long-term renal function is the last crucial finding of this study. According to our data, the

majority of children undergoing CRRT developed some form of chronic kidney dysfunction. Few studies are available on CKD following pediatric AKI and their results appear controversial, with the rate of uncomplete recovery of renal function ranging from 10 to 20% (16, 40). This aspect likely depends on the severity of AKI of analyzed patients (16), their age (41), admission diagnosis (42), and effectiveness of follow-up (43). Interestingly, about 60% of our cohort underwent a post PICU discharge renal referral and follow-up which is higher than recently described (44). This was probably due to the identification of the high severity of renal dysfunction in patients who required dialysis during their PICU admission. In this regard, it would be desirable that close to 100% of AKI children requiring CRRT were referred to the nephrology consultation and follow-up. Unfortunately, this target is far to be reached in clinical practice and very limited information is available in the literature on long-term outcomes of pediatric patients treated with CRRT (45).

Limitations

Several drawbacks should be recognized in this study. Although the relatively small sample size is a major limitation, the single center nature of our study has allowed to accurately describe each patient's clinical presentation at admission and at CRRT initiation, treatment prescription, characteristics, and each circuit lifespan, and also to describe short- and long-term survival and kidney outcome in a precise setting. Unfortunately, we were not able to present data for the entire population of 28 patients who underwent CRRT, but only for the subgroup of 23 patients treated with Prismaflex® machine. Multicenter registries (46) are certainly required for the observation of larger populations. Duration of follow-up was relatively short, and it is possible that longer observation may reveal different outcomes: it is currently unknown if these would imply improvement of further worsening of renal function of these patients. Given the observation nature of this study it is currently unknown if timing of CRRT start, severity of the admission disease, and dose of the analyzed treatment could have affected short and long-term outcomes. However, literature in this field of pediatric critical care nephrology is poor and consistent results should be extrapolated by large databases.

CONCLUSIONS

Our data indicate a low prevalence of CRRT in the PICU population and confirm high morbidity and mortality in these patients. Pediatric CRRT administration is often complicated by unintended discontinuation due to circuit clotting and loss of effective treatment time that should be taken into account early during treatment prescription. Use of adequate vascular accesses and RCA might protect the circuit from clotting. Moreover, despite a relatively short median follow-up time, a great proportion of CRRT patients developed CKD and needed nephrology consult. Once more, this highlights the importance of nephrology referral for these patients, from first CRRT prescription to, more importantly, post-discharge outpatient care.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Meyer Children's Hospital Ethics Committee (registry number 104/2020). Research was performed in line with the principles of the Declaration of Helsinki. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because the Ethics Committee waived informed consent for the analysis and publication.

AUTHOR CONTRIBUTIONS

EB and FG contributed equally to the work, conceived the research idea and the design of the study, were responsible for material preparation and data collection and wrote the first draft of the manuscript. DC and BT contributed to material preparation and data collection. GV was responsible for statistical analysis. SR, ZR, ML'E, and GV contributed to the conception and design of the study. All authors commented on previous versions of the manuscript, read and approved the final manuscript providing substantial contribution as per ICMJE recommendations.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.696798/full#supplementary-material

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REVIEW
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Acute Kidney Injury in Pediatric Diabetic Kidney Disease

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Diabetic kidney disease (DKD) is a common complication of type 1 and 2 diabetes and often presents during adolescence and young adulthood. Given the growing incidence of both type 1 and type 2 diabetes in children and adolescents, DKD represents a significant public health problem. Acute kidney injury (AKI) in youth with diabetes is strongly associated with risk of DKD development. This review will summarize the epidemiology and pathophysiology of AKI in children with diabetes, the relationship between AKI and DKD, and the potential therapeutic interventions. Finally, we will appraise the impact of the recent COVID-19 infection pandemic on AKI in children with diabetes.

Keywords: acute kidney injury, diabetes, diabetic kidney disease, pediatric, COVID-19

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INTRODUCTION

Type 1 diabetes (T1D) has consistently remained one of the most common chronic diseases affecting children and adolescents (1). In the past few decades, the incidence of youth-onset type 2 diabetes (T2D) has also progressively increased, likely due to rising rates of childhood obesity (2). Both types of diabetes are associated with long term complications that result in increased morbidity and mortality (1). Among these complications, diabetic kidney disease (DKD) is associated with the highest rates of excess mortality observed in young persons with diabetes (1). Indeed, DKD represents the leading cause of end-stage kidney disease (ESKD) and dialysis in the developed world (3). The pathophysiology of DKD is multifaceted and is characterized by progressive chronic kidney disease (CKD) (1, 4). In children and adolescents with diabetes, AKI can magnify the risk for CKD development and progression later in life (5–9).

Several mechanisms have been proposed to explain the accentuated risk of acute kidney injury (AKI) in youth with diabetes, including diabetic ketoacidosis (DKA), acute hyperglycemic events, and chronic poor glycemic control (10–12). Hyperglycemia has been shown to directly induce kidney inflammation and tubulopathy (12), while poor glycemic control can lead to polyuria with resultant volume contraction and hypovolemia, which is subsequently associated with the development of pre-renal AKI (11). In this review we seek to appraise the evolving mechanisms, risk-factors, and management strategies for diabetes-induced AKI in the pediatric population.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF AKI IN DIABETES

Epidemiology and Definition of AKI in the Pediatric Population

AKI in youth represents a significant and growing challenge for clinicians, as AKI has been demonstrated in 3.9 out of every 1,000 pediatric hospitalizations at-risk in the U.S. (13), including

up to 64% of hospitalizations for DKA in youth with T1D (14). AKI is currently defined by the Kidney Disease Improving Global Outcomes (KDIGO) consensus classification based on conventional serum creatinine and urine output (UO) criteria (15). Previous widely used classification criteria have also shown an excellent accuracy in screening for AKI in the pediatric population. The pediatric Risk, Injury, Failure, Loss and End-stage Kidney (pRIFLE) criteria, which include a decrease in estimated creatinine clearance (eCCl) per the Schwartz formula over 8 to 24 h and anuria for 12 h (15), and the Acute Kidney Injury Network (16) criteria, which include an increase in serum creatinine over 6 to 24 h and anuria for 12 h (15). The pRIFLE criteria have been shown to have high sensitivity in detecting AKI (16), and the AKIN criteria have demonstrated high specificity (15).

AKI is typically classified into three main categories: pre-renal, intrinsic/renal, and post-renal (17). The most common form of pediatric AKI is pre-renal, a usually reversible form of kidney dysfunction caused by kidney hypoperfusion (18, 19). In the setting of diabetes, the extracellular volume depletion leading to pre-renal AKI is commonly induced by glycosuria because of poorly controlled diabetes (14, 20). The combination of poor glycemic control with pre-renal AKI can eventually lead to intrinsic renal AKI, characterized by structural damage to the renal parenchyma and the occurrence of tubular necrosis (18, 21). Although DKD has historically been considered a glomerular disease, a growing body of evidence suggests that tubular-interstitial injury may be the first alteration in DKD (18, 21). AKI is also divided by severity into stage 1, 2, or 3 with different definitions according to the applied diagnostic criteria for AKI (e.g., pRIFLE AKI stage 1 is defined as a 25% decrease of estimated GFR (eGFR), stage 2 as a decrease of 50%, and stage 3 as a decrease of 75%) (15). Despite a growing body of literature evaluating the incidence and etiologies of AKI in adults, large epidemiologic studies involving pediatric populations with AKI, with or without diabetes, are lacking, as many studies are either limited to a single center or are focused on specific subpopulations (13, 18) (**Table 1**).

Markers of AKI in the Pediatric Population

The diagnosis of AKI, per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, is currently defined by factors including elevated serum creatinine concentration, decreased UO, and renal replacement therapy requirement (32, 33). UO is the oldest known indicator of AKI, yet it retains multiple theoretical advantages over biomarkers such as serum creatinine concentration due to a predefined cut-off value and rapid response to treatment. In contrast, serum creatinine concentration requires comparison to a baseline value which is often either unknown or estimated (34). However, the sole use of UO to diagnose AKI also has several constrains, notably the significant influence of hydration status and blood pressure, the dependence on hemodynamic stability, and the artificial effect of medications such as diuretics and vasopressors (34). Severe glycosuria from uncontrolled diabetes or use of SGLT2 inhibitors can also lead to prerenal or true AKI despite continued UO. Another issue includes the difficulty in accurately measuring UO, particularly in children without Foley catheters in place (34). UO is also not an infallible indicator of AKI as it has been shown that some individuals with severe AKI can still have a preserved UO (34). Serum creatinine concentration is also an imperfect indicator of AKI as it can be delayed and unreliable in the setting of concurrent infections, sepsis, malnutrition, and obesity, which can ultimately lead to an inaccurate diagnosis (34–36). Laboratory and clinical studies are currently targeting the identification of biomarkers that predict the development of early AKI. Some of the most promising AKI biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (lL-18), liver-type fatty-acid-binding protein (L-FABP, also called FABP1), insulin-like-growth-factor-binding protein 7 (IGFBP7), and tissue inhibitor of metalloproteinase 2 (TIMP-2) (37, 38).

NGAL is a protease-resistant polypeptide of the lipocalin superfamily identified in human neutrophils and is expressed by the tubular epithelia of the kidneys in response to inflammation (39–41). NGAL is a promising marker for AKI because it is easily detected in urine or plasma as soon as 1 h following kidney damage and prior to changes in serum creatinine, and it correlates with the severity and duration of AKI (37). Additionally, urine NGAL has been extensively studied in pediatrics and has been shown to be an early and sensitive biomarker for both AKI and DKD (42).

KIM-1, a type-1 transmembrane protein expressed in the renal proximal tubular cells, is significantly upregulated following ischemia (43, 44). In a 2019 study by Assadi and Sharbaf urinary KIM-1 demonstrated the strongest performance for the early detection of AKI among critically ill children with circulatory collapse when compared to NGAL, IL-18, and sCr (45). However, while current evidence supports the use of KIM-1 as a promising new avenue for the detection of AKI, concentrations may be affected by a variety of additional factors including the type of assay, timing and clinical setting of the sample collection, and patient age (46). Similar to NGAL, KIM-1 has also been shown to be elevated in children with diabetes and higher concentrations may associated with the development of early DKD (47).

IL-18 is a cytokine in the IL-1 superfamily that is synthesized by monocytes, macrophages, and proximal tubular epithelial cells of the kidney. Urine IL-18 is currently a promising predictor of early AKI as concentrations increase rapidly after ischemic kidney injury, nearly 12 h before clinical AKI is diagnosed by other means (37). Yet, identification of additional biomarkers for AKI is still necessary as IL-18's accuracy in predicting AKI among children and adolescents is highest when combined with other biomarkers (37).

L-FABP is a cytoplasmic protein involved in intracellular lipid trafficking and endogenous cytoprotection against oxidative stress that is expressed in the proximal epithelial tubular cells of the kidneys (34, 48). Urine L-FABP has been shown to predict both AKI and adverse clinical outcomes in pediatrics, reflecting the negative impact of oxidative stress on the kidneys and the associated resultant proximal tubule cellular injury (38). However, urine L-FABP concentrations may be elevated by factors including obesity, insulin resistance, and high blood pressure, even without concurrent kidney injury (49).

TABLE 1 | Studies on AKI in pediatric populations with and without diabetes.

Study	*n*	Study population	Study aim	Results
Askenazi et al. (8)	174	Children who had previously developed AKI at a single hospital	3–5-year survivorship among children hospitalized with AKI	The 3–5-year survivorship after hospitalization among children with an episode of AKI was 139/174 (79.9%). Thus, patients have a high risk of ongoing residual renal injury and death after AKI
Mammen et al. (9)	126	Children who survived an episode of AKI at a tertiary-care pediatric intensive care unit from 2006 to 2008	Determine the incidence of CKD development following an episode of AKI	13/126 (10.3%) of children developed CKD 1–3 years after AKI. In addition, 59/126 (46.8%) patients were identified as being at risk of CKD
Sutherland et al. (13)	2,644,263	Children in the United States (U.S.) listed in the 2009 Kids Inpatient Database	Characterize pediatric AKI across the U.S. and identify AKI risk factors among a national cohort	AKI occurs in 3.9/1,000 at-risk pediatric hospitalizations. Mortality was highest among neonates and children requiring critical care or dialysis. AKI occurs most commonly with systemic/multiorgan disease
Hursh et al. (14)	165	Children with T1D hospitalized for DKA at a single hospital from 2008 to 2013	Determine the proportion of children hospitalized for DKA who develop AKI, as well as the associated markers of AKI	106/165 (64.2%) of children admitted for DKA had developed AKI. AKI was associated with clinical and biochemical markers of volume depletion and severe acidosis
Kaddourah et al. (22)	4,683	Multinational, prospective study involving pediatric patients admitted to pediatric intensive care units	Define the incremental risk of death and complications associated with severe AKI	AKI developed in 1,261/4,683 patients (26.9%) and severe AKI developed in 543/4,683 patients (11.6%). Death occurred in 60/543 patients (11.0%) with severe AKI vs. 105/4,140 patients (2.5%) without severe AKI. AKI is common and associated with poor outcomes, including increased mortality, among critically ill children and young adults
Baalaaji et al. (23)	79	Children with DKA admitted to a single pediatric intensive care unit (PICU) between 2011 and 2014	Identify the predictors and outcomes of AKI in children	28/79 (35.4%) children developed AKI. 20/28 (71.4%) children with AKI recovered with hydration alone. Serum chloride at 24 h was independently associated with AKI. Children with AKI had prolonged acidosis, longer PICU stay, and higher mortality
Ho et al. (24)	74	Children admitted to a single children's hospital with DKA, with and without AKI, from 2010 to 2018	Assess the influence of intravenous fluid regimens and blood pH on the incidence of AKI in pediatric DKA	There was no statistically significant difference between the volume of IV fluid given to patients with AKI and those without AKI
Charlton et al. (25)	2,110	Neonates admitted to a neonatal intensive care unit who received at least 48 h of intravenous fluids	To assess the risk factors and outcomes of neonatal AKI in the first postnatal week	AKI in the first postnatal week is common and associated with death and longer duration of hospitalization. Risk factors for AKI included resuscitation with epinephrine, admission diagnosis of hyperbilirubinemia, inborn errors of metabolism, and surgical need
Myers et al. (26)	1,255	Children admitted to the Emergency Department with a diagnosis of DKA in 13 United States hospitals	Investigate risk factors for AKI and its association with neurocognitive outcomes in pediatric DKA	AKI occurred in 584/1,359 (43.0%) of DKA episodes. Children with AKI, when compared to those without, had lower scores on tests of short-term memory during DKA. AKI may occur more frequently in children with greater acidosis and circulatory volume depletion during DKA

(Continued)

TABLE 1 | Continued

Study	*n*	Study population	Study aim	Results
Hapca et al. (27)	16,700	Retrospective, cohort study of participants with or without T2D over a median period of 8.2 years	Evaluate rates of AKI and to determine their relationship to CKD status and further kidney function decline	Patients with diabetes have significantly higher rates of AKI compared to patients without diabetes. In addition, patients with diabetes were significantly more likely to have preexisting CKD or CKD that developed during follow-up
Yang et al. (28)	58	Retrospective study performed in a single center from 2004 to 2018 including children admitted with DKA who had T1D	Assess incidence and clinical characteristics of AKI and to identify the associated risk factors of AKI in children with T1D and DKA	AKI frequently occurred in children with T1D who had DKA. Longer duration of TID and elevated anion gap are associated with occurrence of severe AKI
DePiero et al. (29)	1,389	Children diagnosed with DKA in 13-centers from 2011 to 2016	Characterize hemodynamic alterations occurring during DKA and to identify clinical and biochemical factors associated with hypertension	Hypertension occurs in a substantial number of children with DKA (27.8%). Factors associated with hypertension include severe acidosis, AKI, and lower Glasgow Coma Scale scores
Williams et al. (30)	66	Children with DKA in a tertiary care, teaching, and referral hospital	To investigate 0.9% saline compared to Plasma-Lyte-A as an initial fluid in pediatric DKA	The incidence of new or progressive AKI and resolution of AKI were similar in both groups. Plasma-Lyte-A was similar to 0.9% Saline in time to resolution of DKA, need for renal replacement therapy, mortality, and lengths of pediatric intensive care unit and hospital stay
Huang et al. (10)	223	Children presenting with T1D or T2D and DKA between 2000 and 2017	Identify the prevalence of AKI and associations between AKI severity and recovery time from metabolic acidosis	170/223 (56.5%) patients with DKA presented with AKI. Approximately 80% of children with DKA recovered from metabolic acidosis on the first day, regardless of AKI severity
De Zan et al. (31)	811	Children admitted to the pediatric intensive care unit at a single center from 2014 to 2016	Assess the incidence rate of AKI, identify risk factors, and evaluate clinical outcomes	222/811 (27%) patients developed AKI. The most common intensive care admission diagnosis in AKI cases was heart disease (38.6%). Hypoxic ischemia was the most frequent cause of AKI. Risk factors for AKI were multifactorial and were mainly associated with illness severity

AKI, acute kidney injury; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; T1D, type 1 diabetes; T2D, type 2 diabetes.

IGFBP7 and TIMP-2 are cell-cycle arrest proteins expressed in higher concentrations from the renal tubular cells during cellular stress (50). Evaluations of the urinary excretion of TIMP-2 and IGFBP7 have been proven useful in the detection of AKI and the urinary concentration of the product of TIMP-2 and IGFBP7 [(TIMP-2) × (IGFBP7)] was the first urinary AKI biomarker approved by the United States Food and Drug Administration (51). Notably, this biomarker combination has also been validated in post-operative youth following cardiopulmonary bypass, demonstrating accuracy in predicting AKI 6 h after major surgery as well (38).

Other novel biomarkers are currently being investigated for the diagnosis and prognostic stratification of AKI in youth, including microRNAs, urinary low-molecular-weight proteins, and urinary tubular enzymes (37). The validation of these emerging biomarkers in large epidemiological studies is still necessary, but the biomarkers previously discussed hold significant clinical promise as supplements to our current tools for the identification of AKI in youth, namely serum creatinine concentration and UO.

Pathophysiologic Mechanisms of AKI in Youth With Diabetes

The pathophysiologic mechanisms leading to diabetes-induced kidney injury are complex and oftentimes multifactorial (**Figure 1**). Structural and functional changes in the endothelial cells of the vasculature and the epithelial cells of the kidney tubules have been postulated to promote the production of cytokines and chemokines, which induce inflammation, ischemic tubular epithelial and endothelial injury, and isolated proximal tubulopathy (19, 52, 53).

Risk factors for the development of AKI in children and adolescents with diabetes are numerous and include, but are not limited to, episodes of DKA as well as the presence of acute and chronic hyperglycemia. DKA is a severe risk factor for the development of AKI, particularly in youth with T1D, and

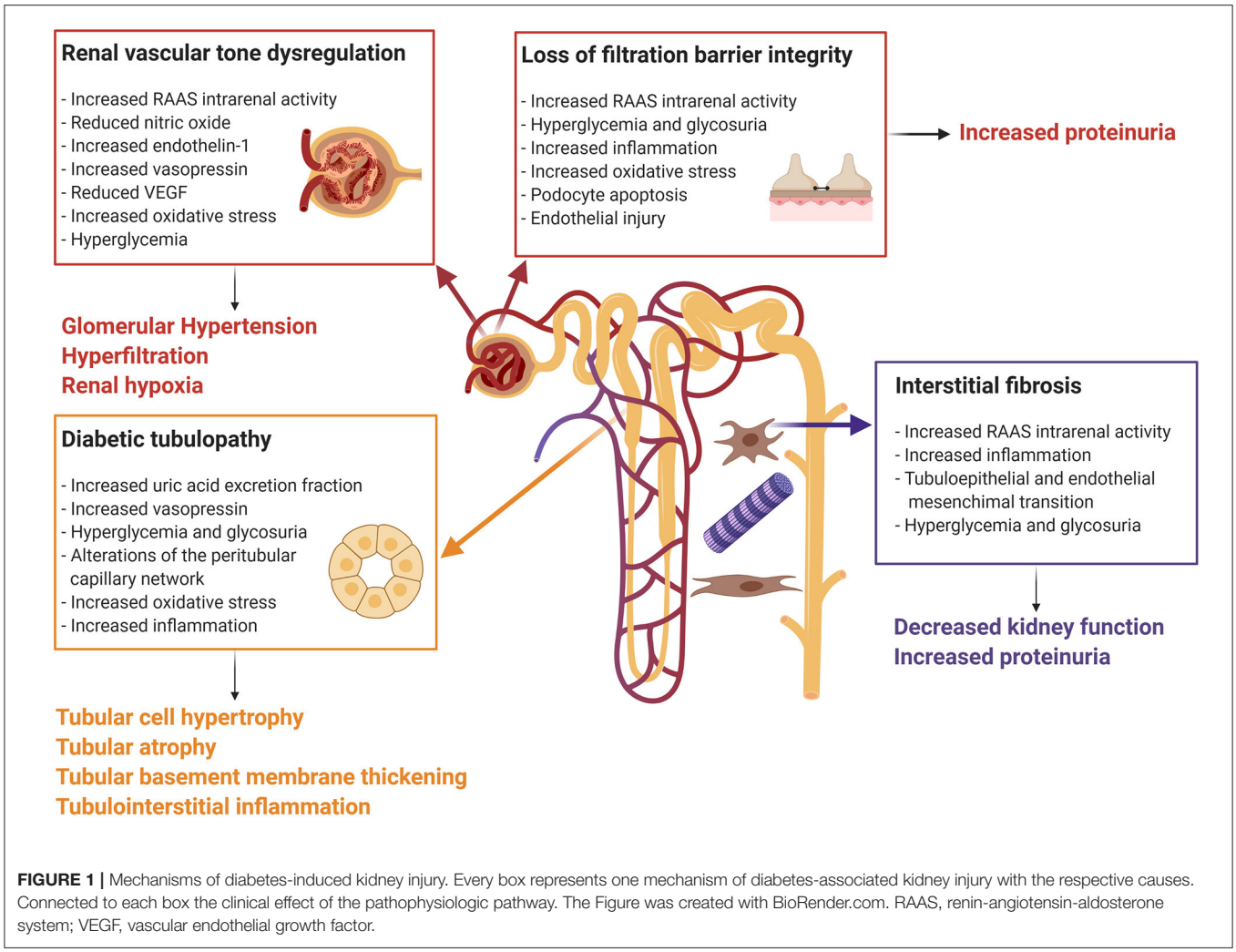

FIGURE 1 | Mechanisms of diabetes-induced kidney injury. Every box represents one mechanism of diabetes-associated kidney injury with the respective causes. Connected to each box the clinical effect of the pathophysiologic pathway. The Figure was created with BioRender.com. RAAS, renin-angiotensin-aldosterone system; VEGF, vascular endothelial growth factor.

is characterized by a combination of hyperglycemia, metabolic acidosis, and the production of ketone bodies (54, 55). DKA is currently the leading cause of hospitalization, morbidity, and mortality in youth with T1D (14, 56, 57) and in a study by Hursh et al. up to 64% of youth with T1D hospitalized for DKA developed AKI (14). This percentage increased to 85% if the individual required admission to the Intensive Care Unit (14). Severe hyperglycemia associated with DKA leads to osmotic diuresis, dehydration, and significant pre-renal AKI (54, 55).

Additionally, DKA has also been associated with early tubulopathy that may be caused by dysregulation of uric acid and vasopressin (58–62). Indeed, a recent study by Burckhardt et al. found that copeptin, a surrogate marker for vasopressin, was elevated in children with DKA (63). Elevated copeptin concentrations have also been associated with markers of tubular injury and an increased risk for the development of DKD (62, 64). We have previously demonstrated that adults with T1D and DKD had higher concentrations of copeptin compared to both healthy controls and adults with T1D without DKD (65). Furthermore, elevations in copeptin are more strongly correlated with intrarenal renin-angiotensin-aldosterone system (RAAS) activation in individuals with T1D compared to healthy controls (65). We have also demonstrated in a study of 169 adolescents with T1D that adolescents with T1D in the highest tertile of copeptin concentration had a significantly higher urinary albumin-to-creatinine ratio compared to those in the lowest tertile (66). Furthermore, several studies have shown that chronically elevated vasopressin can exacerbate kidney injury in animal models (67, 68).

Thus, we hypothesize that vasopressin dysregulation may increase the risk of AKI during an episode of DKA and may subsequently accentuate the risk for future DKD. Activation of the intrarenal RAAS has been shown to impact regulation of renal vascular tone and children and adolescents with T1D and T2D have demonstrated greater resistance indexes when compared to their healthy peers without diabetes (69–71). Additionally, nitric oxide (NO), endothelin-1 (ET-1), vasopressin, and vascular endothelial growth factor (VEGF) have also been shown to be impaired as regulators of kidney vascular tone in individuals with diabetes (58, 65, 72–74).

Dysregulation of kidney vascular endothelial tone secondary to poor glycemic control is thought to be primarily responsible for the development of glomerular hyperfiltration, a common early finding in young persons with diabetes (75, 76). Persistent glomerular hyperfiltration leads to the development of intraglomerular hypertension and subsequent glomerulosclerosis which results in a progressive impairment in kidney function and eventual DKD (75, 76). A dysregulation in baseline kidney vascular tone may accelerate the damage due to AKI, particularly in the setting of pre-renal AKI where the body relies on changes in kidney vascular resistance to maintain blood pressure (18, 19). Kidney hypoperfusion secondary to dehydration or shock also can be significantly worsened by the absence of an appropriate counterregulatory vascular response to maintain kidney blood flow (75, 76). Consequently, the incidence of AKI in the setting of sepsis has been found to be significantly higher in people with diabetes compared to people without diabetes (4, 77).

Hyperuricemia may also contribute to the development of diabetes-related acute and chronic kidney disease (60). High uric acid concentrations have been shown to induce both a crystal-mediated and crystal-independent nephropathy, with the additional development of tubulointerstitial fibrosis, proximal tubulopathy, and glomerular hypertension (61, 78). Elevations in serum uric acid concentrations have also been associated with the development of AKI and medications that lower serum uric acid concentrations have demonstrated a potential to reduce the incidence of AKI (79–82). However, it is important to note that elevated uric acid concentrations may be due to dehydration that may directly induce kidney injury. We have previously demonstrated that youth with T1D and hyperfiltration had a higher urinary fractional uric acid excretion compared to both healthy controls and peers with T1D who have normofiltration (81). Additionally, overweight and obese youth with T1D demonstrated a stronger negative correlation between serum uric acid concentrations and eGFR when compared to their normal weight peers with T1D (83). Thus, high serum uric acid concentrations exhibit a clear association with AKI. Additionally, not only do young persons with diabetes have higher baseline concentrations of serum uric acid, they also demonstrate a stronger association between elevations in uric acid concentration and impaired kidney function.

Another pathophysiologic pathway that has been shown to greatly contribute to the development of diabetes-induced AKI is the presence of persistent hyperglycemia, a hallmark of diabetes. The degree of persistent hyperglycemia has been shown to correlate with longer durations of stay in the intensive care unit as well as an increased risk for the development of AKI which can eventually lead to both CKD and ESKD (4, 12, 78). Notably, laboratory studies have demonstrated endothelial cell apoptosis, interstitial vascular rarefaction, mitochondrial dysfunction, proximal tubular cell inflammation, profibrogenic cytokine secretion, and podocyte apoptosis and autophagy in response to hyperglycemia (4).

Among the glomerular endothelial cells, hyperglycemia also induces cellular apoptosis via the Nuclear Factor-κB (NF-κB) and c-Jun NH2-terminal kinase (JNK) pathways (84, 85) and causes interstitial vascular rarefaction which leads to kidney hypoxic injury and can compromise the generation of necessary ATP (86). Overproduction of reactive oxygen species (ROS) has also been shown to induce endothelial cell damage and reduce the amount of nitric oxide available to modulate vascular tone, thereby contributing to dysregulation of sympathetic tone and sodium homeostasis in the kidneys (87).

Mitochondrial dysfunction has also been identified in the proximal tubules of individuals with diabetes during states of kidney hypoxia, further delaying future recovery from kidney injury (88). Furthermore, in diabetic rat models, the enzyme Myo-inositol oxygenase (MIOX) is upregulated in the setting of mitochondrial dysfunction, thereby inducing ROS production, cellular apoptosis, and eventually, DKD (89). MIOX is modulated by specificity protein-1 (Sp-1), a transcription factor which could serve as a potential site for the development of interventions targeting the progression of DKD as inhibition of Sp-1 has been shown to reduce ROS production (90).

Inflammatory cytokines in the proximal tubule have also been shown to play a significant role in the progression of AKI to diabetes-related CKD. Tissue necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 have been reported to be upregulated in the setting of diabetes-related CKD and are known to stimulate an inflammatory cascade that contributes to the progression of CKD (91–94). Hyperglycemia has also been shown to induce the expression of adhesion molecules and chemokines in proximal tubular cells that result in inflammation, fibrosis, and kidney injury (95, 96). Additionally, a maladaptive compensatory response for this hyperglycemia-induced inflammatory cascade in the proximal tubule leads to a profibrogenic cytokine secretion and subsequent fibrosis that plays a significant role in the transition of AKI to CKD (97). It has been demonstrated that proximal tubular cells cultured in hyperglycemic media secrete transforming growth factor beta (TGF-β)-dependent extracellular matrix (98, 99) and activation of this pathway, which plays a central role in mediating kidney fibrosis, has been shown to be significantly upregulated in both diabetic rat models and biopsies from humans with diabetes (100). Hyperglycemia has also induced podocyte apoptosis in murine models of diabetes and in adults with T2D, leading to kidney injury and future diabetes-related CKD. Podocyte apoptosis in the setting of hyperglycemia occurs through mechanisms that include, but are not limited to, increased ROS, RAAS activation, and upregulation of the mammalian target of rapamycin (mTOR) pathway (4, 101–105). However, unlike hyperglycemia-induced injury to the proximal tubule cells of the kidney, podocyte apoptosis in DKD is likely irreversible and leads to permanent damage (106).

Risk of AKI in the Pediatric Population With Diabetes

Risk factors for AKI are numerous and include concurrent hospitalizations and comorbid conditions such as hypertension and diabetes. Diabetes is an important risk factor for AKI as it has been shown to independently associate with longer hospitalizations, increased severity of concomitant infections, and future development of CKD (5, 107–112). Indeed, there is

a strong association between AKI, CKD, and ESKD (4, 6, 113–115), as it has been demonstrated that both single and repetitive episodes of AKI significantly increase the risk for developing CKD in youth and adults with diabetes (5–9). Additionally, the incidence of AKI is further compounded by factors including surgical interventions (116–120), aminoglycoside usage (121), and sepsis (4, 77), and this occurs to a greater degree in individuals with vs. without diabetes. Yet, while AKI and CKD remain strongly interconnected, as evidenced by a robust body of literature detailing the transition from AKI to CKD, the effects of AKI on CKD are less clear, thus resulting in a disproportionate focus on CKD vs. AKI in diabetes research (4, 13, 34).

THERAPEUTIC STRATEGIES AND IMPLICATIONS

To date, there is no universal effective therapy for AKI. As AKI is the result of different pathophysiologic mechanisms, the treatment consists of addressing the underlying causes (e.g., dehydration), correcting the hydro-electrolyte imbalances, withdrawing potential nephrotoxins, starting diuretics, and, when needed, renal replacement therapy (122). As previously mentioned, children with diabetes and DKD have a higher risk of developing AKI. In this paragraph we will discuss how DKD therapeutic strategies may impact the risk of AKI in youth with diabetes.

RAAS inhibitors, in addition to strategies that target euglycemia and minimize cardiovascular risk factors, remain the cornerstone of our existing treatment methods for DKD and has shown to attenuate proteinuria (123–125). In the SEARCH for Diabetes in Youth (SEARCH) study, youth with T2D were found to have significantly higher urinary albumin-to-creatinine ratios than youth with T1D (126), and this difference remained significant after multivariable adjustment for obesity, hypertension, and dyslipidemia, all known risk factors for DKD that are more prevalent in youth with T2D vs. T1D (126). Consequently, due to known differences in risk for the development of DKD, treatment of youth with T2D with RAAS inhibitors may be more frequently indicated than treatment of youth with T1D. However, RAAS inhibitors should be withdraw during AKI due to their effects on intrarenal hemodynamic function as well as potential direct nephrotoxic effect, which could magnify the acute kidney insult (123–125).

In addition to glucose-lowering effects, many anti-hyperglycemic agents available today also showcase significant nephroprotective properties in DKD. To date, anti-hyperglycemic agents that have demonstrated nephroprotective properties include metformin and thiazolidinediones, as well as newer classes of glycemic-lowering agents including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium/glucose cotransporter 2 (SGLT2) inhibitors (127–129). Insulin, metformin and GLP-1 receptor agonists are the only medications approved for diabetes treatment in children in the US. Despite being widely used in the of the management of patients with diabetes-related CKD, metformin has been shown to accumulate in the setting of an impaired eGFR (e.g., 30–60 mL/min/1.73 m^2), thereby causing toxicity that can lead to impairments in mitochondrial function and possible non-hypoxic type B lactic acidosis (130). Thiazolidinediones, such as pioglitazone, are insulin sensitizing agents that target Peroxisome Proliferators Activated Receptors (PPARs) to regulate gene expression and thereby decrease hepatic gluconeogenesis, increase adiponectin concentrations, and increase insulin-dependent glucose uptake in muscle and fat tissues (131). Studies have previously demonstrated a possible role for PPARs in the protection against AKI (132–134) and a large meta-analysis reported an association between treatment with thiazolidinediones and a significant decrease in urinary albumin excretion (129). Yet, no randomized controlled trials have been completed to thoroughly explore the acute and chronic kidney protective effects of thiazolidinediones (135). Next, some studies have also suggested beneficial nephroprotective effects for both DPP-4 inhibitors and GLP-1 receptor agonists (127, 136). However, a recent Cochrane review was less definitive and concluded that the known effects of DPP-4 inhibitors and GLP-1 receptor agonists on eGFR are uncertain (136). Additionally, SGLT2 inhibitors have been shown to be beneficial in the prevention of AKI in two different randomized, placebo-controlled trials: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) (137, 138). However, similarly to DPP-4 inhibitors and GLP-1 receptor agonists, a recent Cochrane review found that SGLT2 inhibitors had little to no effect on the risk for AKI (136).

Several ongoing or recently terminated trials have also analyzed the effects of other classes of drugs, particularly those targeting the kidney vasculature and the complex homeostatic mechanisms of vasoconstriction and vasodilation, in the prevention and treatment of DKD (74). Several compounds have shown promise with possible nephroprotective effects against both AKI and CKD; however, many of the human trials are still ongoing and most exclude pediatric participants. In animal models, endothelin receptor antagonists, PPAR agonists, phosphodiesterase inhibitors, and novel mineralocorticoid receptor blockers have demonstrated possible nephroprotective effects against AKI and may represent future therapeutic strategies for the prevention and treatment of AKI and CKD (123, 139–142). In particular, finerenone, a non-steroidal selective mineralocorticoid receptor antagonist, has recently been shown to reduce the risk of CKD progression in adults with T2D in the Efficacy and Safety of Finerenone in Subjects with Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) study (143). Notably, finerenone was also able to prevent the transition from AKI to CKD in animal models and could represent an early therapeutic intervention for individuals demonstrating AKI to prevent long term complications (144).

In summary, in addition to known anti-hyperglycemic effects, many glucose-lowering agents have also demonstrated evidence of nephroprotection against both diabetes-associated AKI and CKD, two comorbidities that significantly increase the risk of morbidity and mortality in youth with diabetes. Additionally, newer classes of drugs that target intrarenal hemodynamic

dysfunction in children and adolescents with diabetes are a promising new avenue for the treatment of both AKI and CKD. Consequently, well-designed pediatric trials are warranted to address the steadily increasing burden of AKI in children and adolescents with diabetes and subsequently prevent the development and progression of chronic DKD.

COVID-19 IMPACT

Epidemiologic studies have demonstrated evidence of AKI in more than 35% of adults who are hospitalized for the novel coronavirus disease 2019 (COVID-19) (145, 146). The prevalence of diabetes in patients with COVID-19 varies from 5 to 58% (147), yet patients with diabetes are far more likely to develop severe COVID-19 and consequent AKI than their counterparts without diabetes, with a prevalence of critical disease varying from 14 to 32% in adults with diabetes and COVID-19 (147). Acute proximal tubular damage, collapsing glomerulopathy, and podocyte injury have been found to be pathologic hallmarks of kidney injury in adults with confirmed COVID-19 (148–150).

In contrast, AKI in youth with COVID-19 has mostly been described as a consequence of dehydration secondary to gastrointestinal side effects (151, 152). One possible explanation that has been proposed is the presence of immature angiotensin converting enzyme 2 (ACE2) receptors in children and adolescents (151). ACE2 receptors are expressed in both the proximal tubular cells and podocytes and thus may be a site of cytokine-mediated effects as a result of a heightened immune system response in the setting of an active COVID-19 infection (149, 153). However, COVID-19-induced effects on the ACE2 receptor may not fully describe the AKI seen in children and adolescents with COVID-19 as other factors including the presence of a cytokine storm and/or a pro-coagulative state have also been shown to be independently associated with AKI in the setting of COVID-19 (145, 151). This finding has been corroborated by evidence of a close temporal relationship between the development of AKI and impending respiratory failure in patients with COVID-19 (145).

Thus, while AKI remains a somewhat rare complication of COVID-19 infection in pediatrics, it is notable that a concurrent diagnosis of diabetes increases the risk of associated kidney injury. Methods to assist with rapid diagnosis and treatment of AKI in youth, particularly in those with diabetes, could prevent further AKI progression and help mitigate the risk of future CKD development.

AUTHOR CONTRIBUTIONS

FP, TR, and PB contributed to the conception and design of the review paper. All authors contributed to the manuscript revision, read, and approved the submitted version.

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REVIEW
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Two to Tango: Kidney-Lung Interaction in Acute Kidney Injury and Acute Respiratory Distress Syndrome

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Acute Kidney Injury (AKI) is an independent risk factor for mortality in hospitalized patients. AKI syndrome leads to fluid overload, electrolyte and acid-base disturbances, immunoparalysis, and propagates multiple organ dysfunction through organ "crosstalk". Preclinical models suggest AKI causes acute lung injury (ALI), and conversely, mechanical ventilation and ALI cause AKI. In the clinical setting, respiratory complications are a key driver of increased mortality in patients with AKI, highlighting the bidirectional relationship. This article highlights the challenging and complex interactions between the lung and kidney in critically ill patients with AKI and acute respiratory distress syndrome (ARDS) and global implications of AKI. We discuss disease-specific molecular mediators and inflammatory pathways involved in organ crosstalk in the AKI-ARDS construct, and highlight the reciprocal hemodynamic effects of elevated pulmonary vascular resistance and central venous pressure (CVP) leading to renal hypoperfusion and pulmonary edema associated with fluid overload and increased right ventricular afterload. Finally, we discuss the notion of different ARDS "phenotypes" and the response to fluid overload, suggesting differential organ crosstalk in specific pathological states. While the directionality of effect remains challenging to distinguish at the bedside due to lag in diagnosis with conventional renal function markers and lack of tangible damage markers, this review provides a paradigm for understanding kidney-lung interactions in the critically ill patient.

Keywords: AKI, ARDS, lung, PARDS, fluid overload

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a life-threatening condition and a leading cause of mortality in critically ill patients causing nearly 200,000 deaths in the United States each year (1). The development of acute kidney injury (AKI) is common in patients with ARDS. AKI significantly adds to the morbidity and mortality of patients with ARDS. In the ARDSNet trial, patients with AKI and ARDS had almost twice the mortality rate than those with ARDS alone (2).

The implications of AKI are broad and include fluid overload, electrolyte abnormalities, immunoparalysis, and multiple organ dysfunction through organ crosstalk. Respiratory complications are a key marker of increased mortality in patients with AKI, which points to a biologically plausible mechanistic link between AKI and Acute Lung Injury (ALI).

Animal models show AKI causes ALI (3). Conversely, mechanical ventilation and ALI can lead to AKI, further supporting a bidirectional relationship (4).

There are many challenging and complex interactions between the lung and kidney in critically ill patients with AKI and ARDS (**Figure 1**). These include disease specific molecular mediators and inflammatory pathways unique to ARDS and AKI that are involved in organ crosstalk. Additionally, there are patient characteristics such as hemodynamics, comorbidities, and host factors such as genetic susceptibility in AKI that can lead to worsening ARDS. Recently, different ARDS "phenotypes" have been proposed via utilization of unsupervised clustering with or without the combination of unique biomarkers (1, 5). An intriguing aspect of these models has been demonstration of a differential response to fluid, which might suggest discrete mechanisms of organ crosstalk in specific pathological states. Finally, there are likely reciprocal hemodynamic effects of elevated pulmonary vascular resistance and central venous pressure (CVP) leading to renal hypoperfusion and pulmonary edema associated with fluid overload, which could lead to increased right ventricular afterload. Each of these interactions contribute to the ARDS-AKI construct and highlight how the implications of AKI go beyond just the kidney. The directionality of effect remains challenging to distinguish at bedside due to a lag in diagnosis with conventional renal function markers and lack of tangible damage markers in both AKI and ARDS. Thus, it is important to have an in depth understanding of this relationship. This review provides a paradigm for understanding the kidney-lung interactions in critically ill patients.

KIDNEY MEDIATED LUNG INJURY

Elucidation of the pathophysiology of AKI has revealed a complex, multisystem disorder with clinically important implications for patients with AKI. Important among these is the relationship between AKI, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Data from studies in multiple clinical settings and animal models support a dynamic interplay between the kidneys and lungs with each set of organs having the potential to influence and disrupt the structure and function of the other (**Table 1**). In the setting of AKI, injury to the kidneys can have distant effects on the lungs through both cellular and circulating biochemical mediators. These warrant further investigation as biomarkers and potential therapeutic targets and include both inflammatory and non-inflammatory mediators.

Inflammatory Mediators of ARDS in the Setting of AKI

Cellular Inflammatory Mediators

Several populations of immune cells, including T-cells, neutrophils and macrophages, have been shown to mediate lung injury in the setting of AKI. Evidence for the involvement

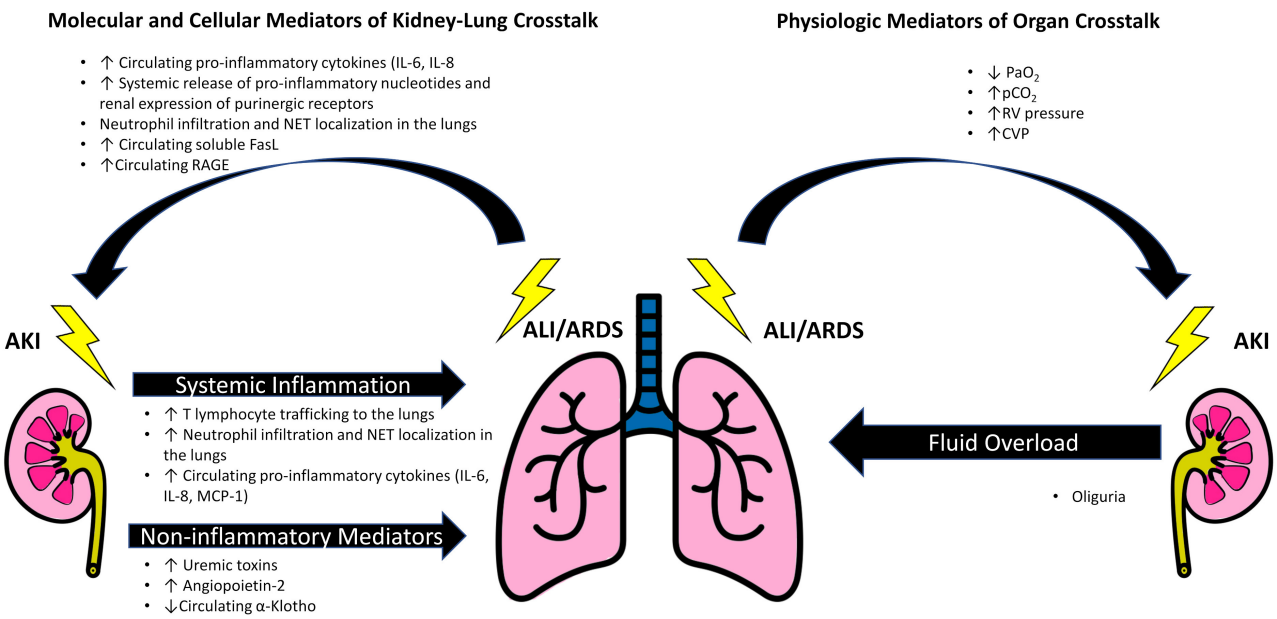

FIGURE 1 | Schematic of mediators of kidney-lung crosstalk in AKI and ARDS. Acute kidney injury propagates acute lung injury and contributes to the development of acute respiratory distress syndrome (ARDS) by generation of inflammatory cytokines, such as IL-6, increased trafficking of T lymphocytes and neutrophils to the lungs. Additionally, AKI can contribute to the development of pulmonary edema and ARDS due to the combination of fluid overload, changes in expression of pulmonary epithelial Na channels and aquaporin-5 mediated by uremic toxins, and angiopoietin-2 induced vascular leak. A reduction in circulating α-Klotho after AKI increases the lungs' susceptibility to oxidative damage. Factors that promote renal injury after ALI/ARDS include a systemic inflammatory response associated with mechanical ventilation. Key lung mediated factors include IL-6, nucleotides, and soluble receptor for advanced glycation end products (RAGE). Increased circulating FasL induces renal tubular epithelial cell apoptosis. Additionally, the ALI/ARDS may reduce renal blood flow through the effects of hypoxia and hypercapnia on intrarenal vasculature, as well by the direct action of elevated right ventricular and central venous pressures in opposition to renal perfusion.

TABLE 1 | Selected publications highlighting kidney mediated lung injury.

Authors	Key findings
Inflammatory mediators of lung injury	
Lie et al. (6)	Renal ischemia-reperfusion injury is associated pulmonary epithelial cell apoptosis mediated by increased trafficking of CD8+ T lymphocytes to the lungs
Nakazawa et al. (7)	Renal ischemia-reperfusion injury leads to increased neutrophil extracellular trap formation in the lungs and is associated with pulmonary epithelial cell apoptosis
Klein et al. (3) Ahuja et al. (8)	IL-6 deletion or blockade attenuate lung inflammation and injury after renal ischemia-reperfusion injury (mouse model)
Non-inflammatory mediators of lung injury	
Rabb et al. (9)	Renal ischemia-reperfusion injury and bilateral nephrectomy are associated with pulmonary edema and altered expression of the pulmonary epithelial Na channel and aquaporin-5
Yabuuchi et al. (10)	The uremic toxin indoxyl sulfate accumulates in the lungs after renal ischemia-reperfusion injury and induces altered pulmonary expression of aquaporin-5
Hsia et al. (11)	Supplementation with alpha Klotho, which is normally decreased after AKI, attenuates lung damage after renal ischemia-reperfusion injury
de Vries et al. (12)	Renal ischemia-reperfusion injury releases systemic angiopoietin-2
Zinter et al. (13)	Elevated plasma angiopoietin-2 concentration is associated with increased mortality in children with ARDS
Alobaidi et al. (14)	Fluid overload is associated with mortality in critically ill children

of T-cells in distant organ effects in the setting of AKI comes initially from investigation of the actions of T cells following organ specific injury. For example, in a mouse model of ischemia-reperfusion AKI, T-cell trafficking to the injured kidney has been shown to occur within 1 hour of the time of insult and to result in the local release of proinflammatory mediators (15). Furthermore, a major target of this T-cell recruitment and proinflammatory activation are endothelial cells, resulting in disruption of the renal microvascular barrier and an increase in renal microvascular permeability (15, 16). Extending these findings to potential mechanisms of T-cell mediated lung injury in AKI, Lie et al. examined T-cell trafficking and activation in a mouse model of ischemic AKI and found that, compared to sham controls, the number of T-cells, specifically CD8+ T-cells, was significantly increased in the lungs of mice with ischemic AKI (6). In addition, markers of T-cell activation were also increased (6). Together, these findings suggest that in AKI, T-cells are not only targeted to the lungs but also that these T-cells display markers of activation at the time of infiltration into the lungs. This study also showed that T-cells mediate pulmonary cell apoptosis, as evidenced by an increase in caspase-3 activity in the pulmonary tissue of mice following ischemic AKI, and that this pulmonary apoptosis results in disruption of the pulmonary microvascular barrier shown by increased bronchoalveolar lavage (BAL) total protein (6). Interestingly, this apoptotic effect was not present in T-cell depleted mice and was restored by adoptive transfer and reconstitution of T cells in the T-cell deficient mice (6). In aggregate, these animal model findings highlight the influence of T-cells not only in modulating injury to the kidney in AKI but also show the impact that T-cell trafficking, and activation can have on the lungs in the setting of AKI.

Similar to T-cells, both neutrophils and macrophages have been shown to be involved in the mediation of organ specific injury in both the kidney and the lung. In several models of AKI, including ischemia and nephrotoxin associated AKI, resident renal macrophages are involved in the initial response to injury and are targeted to the sites of injury through the release of damage associated molecular pattern (DAMP) molecules and hypoxia inducible factors (HIFs) from injured renal tubular epithelial cells (17, 18). This process occurs relatively quickly during the first 24 hours following injury (19), and subsequently, these recruited macrophages perpetuate the inflammatory response by recruiting other leukocytes including bone marrow derived macrophages, neutrophils, and lymphocytes through the secretion of proinflammatory signal molecules, such as tumor necrosis factor-alpha (TNF-α) (20, 21). The next steps in the macrophage response to tissue injury in AKI involve the regulation of inflammation and a shift in macrophage subtype from M1 macrophages that promote the initial rapid inflammatory response to the M2 subtype which move towards tissue repair (22).

Similar macrophage and neutrophil driven processes occur in ARDS, and highlight the importance of the balance between initial rapid pro-inflammatory phase, and the subsequent regulation of inflammation and shift to a more reparative milieu. One important neutrophil related intersection of AKI and ALI could be at the formation of neutrophil extracellular traps (NETs). NET formation is a unique form of bacterial killing and is important to the normal response to microbial infection, but it also has been shown to occur at sites of sterile inflammation including the development of AKI and ALI/ARDS (23, 24). Interestingly, in a mouse model of ischemic AKI, NET formation was not only shown to amplify kidney damage, but NET levels and apoptosis were also increased in the lungs, suggesting a role for NETs as a circulating factor mediating ALI/ARDS following AKI (7). While an appropriately targeted cellular response to tissue injury is a critically important adaptive response, the above noted data support the idea that a dysregulated and exaggerated inflammatory response can potentially worsen not only local tissue damage at the initial

site of injury, but also might cause injury at distant sites in other organs.

Soluble Inflammatory Mediators

In addition to cellular mediators of tissue injury, several soluble factors have been reported to trigger ARDS in the setting of AKI. Similar to the cell driven inflammatory responses outlined above, these inflammatory molecules have been shown to mediate damage not only locally but also have been implicated in distant organ effects including causing ALI in the setting of AKI (25).

Important among the molecular mediators of lung injury associated with AKI is interleukin-6 (IL-6). Clinically, serum IL-6 levels have been shown to increase in patients following AKI, and also have been associated with prolonged mechanical ventilation in the setting of AKI (26). Regarding the pulmonary effects of IL-6 in AKI, a study by Klein et al. showed increased pulmonary inflammation, increased neutrophil recruitment to the lungs, and increased pulmonary capillary leak using a mouse model of renal ischemic injury and also in a bilateral nephrectomy model (3). In this model, IL-6 deficient mice and mice treated with IL-6 antibody showed an attenuated lung inflammatory response following AKI despite similar levels of renal dysfunction (3). As a corollary to this, intravenous injection of IL-6 to IL-6 deficient mice has been shown to restore lung inflammation implicating circulating, and not local pulmonary, IL-6 in driving pulmonary inflammation following AKI (8). Intriguingly, inhaled IL-6 might actually provide a protective effect for the lungs compared with circulating IL-6, highlighting circulating IL-6 as a mediator of distant lung injury after AKI (27).

Similar to IL-6, interleukin-8 (IL-8) has been studied with regard to its involvement in tissue specific injury in AKI and ALI as well as in AKI mediated lung injury. There is evidence that IL-8 is increased in the serum of patients with AKI following cardiac surgery, and that this elevation in IL-8 is associated with prolonged mechanical ventilation (26). Also similar to IL-6, mice deficient in CXCL1, the mouse functional analog of human IL-8, or treated with anti CXCL1 antibodies, have been shown to be protected from AKI associated lung injury (8, 28). In this way, both circulating IL-6 and IL-8 are shown to play a strong role in generating and perpetuating injury to the lungs following AKI.

In contrast to IL-6 and IL-8, other circulating cytokines appear to play a more anti-inflammatory role in modulating lung injury following AKI. In a mouse model of AKI using bilateral nephrectomy, treatment with IL-10 was shown to decrease pulmonary edema, neutrophil infiltration and BAL fluid protein, indicating a protective effect of IL-10 on the lungs of these experimental animals with AKI (29). Conflicting data exist on the impact of extracorporeal blood purification and its impact on mitigation of these mechanisms of kidney and lung injury, a complete review of this topic is beyond the scope of this manuscript.

Non-inflammatory Mediators of ARDS in the Setting of AKI

Uremic Lung: Resurrecting an Old Idea

The link between AKI and subsequent ARDS was first recognized in the mid-20th century when clinicians coined the term "uremic lung" (30). While this antiquated nomenclature has fallen into disuse, it was in fact quite prescient because it encapsulates the role of uremic toxins in kidney lung crosstalk. Uremic toxins such as indoxyl sulfate and p-cresyl sulfate contribute to the development of ARDS via their pro-inflammatory effects and through direct effects on pulmonary gene expression leading to dysregulated fluid handling in the lungs. While induction of pro-inflammatory genes in the lung and histologic evidence of pulmonary inflammation is more severe after renal ischemia reperfusion injury, mice that undergo bilateral nephrectomy also demonstrate increased pulmonary expression of *TNFa, IL-6,* and *CXLCL-1* (3, 31, 32). In fact, lung injury in nephrectomized mice is markedly attenuated in IL-6 knockouts or treatment with an IL-6 neutralizing antibody (3). However, the proinflammatory effects of bilateral nephrectomy may not be solely explained by reduced clearance of IL-6, since more recent studies have shown that indoxyl sulfate is a potent inducer of IL-6 expression through the aryl hydrocarbon receptor and NFκB pathways (33–35). In addition to their proinflammatory effects, uremic toxins accumulate in the lungs and pleural fluid where they contribute to the development of non-cardiogenic pulmonary edema by dysregulated Na and water clearance via downregulated expression of epithelial Na channels, the Na,K ATPase, and aquaporins-1 and -5 (9, 10, 36, 37). Finally, uremic toxins are well-known inducers of endothelial dysfunction, which is mediated by increased reactive oxygen species production and downregulation of antioxidant genes such as *Nrf-2*, *α-Klotho, and Heme oxygenase-1* and have been implicated as proinflammatory mediators of endothelial dysfunction (38). While this has not been demonstrated specifically in the pulmonary vasculature, it is biologically plausible that endothelial dysfunction caused by uremic toxins contributes to pulmonary vascular leak. Therefore, uremic toxins can contribute to the development of ARDS by several mechanisms, and future studies should investigate the ability of these biomarkers to identify patients with AKI who are at risk of developing pulmonary complications.

α-Klotho

α-Klotho has recently emerged as an important mediator of kidney-lung crosstalk in the setting of AKI. Initially identified as an anti-aging gene, disruption of α-Klotho expression in mice leads to early death due to progressive multi-organ failure that resembles accelerated aging and is associated with emphysematous changes in the lung (39). However, α-Klotho is not expressed in the lung, its expression is restricted predominantly to the kidney and parathyroid glands, where it functions as the co-receptor for FGF-23, a hormone that is a critical regulator of phosphate metabolism (40, 41). α-Klotho exists as both a type-I single pass transmembrane protein and a soluble form, which is generated either by alternative splicing or proteolytic cleavage of the ectodomain of the membrane bound form (42, 43). Soluble α-Klotho has pleiotropic cytoprotective effects and is predominantly derived from the kidney (11, 44, 45). Of note, AKI leads to a precipitous decrease in soluble α-Klotho, and in a rodent model of ARDS after AKI, repletion of α-Klotho provided protection of subsequent oxidative lung injury through upregulation of downstream antioxidant effectors of the Nrf2

TABLE 2 | Selected publications highlighting lung mediated renal injury.

Authors	Key findings
Effects of hypoxemia and hypercapnea on renal perfusion	
Darmon et al. (60)	Hypoxemia reduces renal perfusion, increases renal resistive index
Sharkey et al. (61)	Hypoxia and hypercapnia increase renal resistive index and reduce renal perfusion independent of the sympathetic nervous system
Renal hemodynamic effects of ARDS	
Ottolina et al. (62)	Higher PEEP is associated with increased risk of AKI in patients with COVID-19
Inflammatory mediators of kidney injury	
Douillet et al. (63)	Mechanical ventilation induces release of nucleotides from pulmonary tissue and altered expression of purinoreceptors in the kidneys
Imai et al. (4)	Injurious mechanical ventilation strategies increase systemic levels of inflammatory cytokines, chemokines, and soluble FasL is associated with proximal tubule epithelial cell apoptosis
Ranieri et al. (64)	Effect of mechanical ventilation on systemic and local production of inflammatory cytokines
Parsons et al. (65)	Lung-protective ventilation strategy reduces systemic levels of proinflammatory cytokines
Calfee et al. (66)	Acute lung injury is associated with increased plasma concentration of receptor for advanced glycation end products (RAGE)
Subphenotypes of ARDS	
Calfee et al. (67)	Identification of ARDS subphenotypes using molecular phenotyping
Famous et al. (5)	Differential response of ARDS subphenotypes respond to fluid management

pathway (46–49). Therefore, α-Klotho has been proposed both as a biomarker for predicting the development of AKI-induced ARDS and as a potential therapeutic target.

Angiopoietin-2 – Endothelial Damage Marker

Angiopoietin-2 (Ang-2) has been identified as a mediator of vascular permeability in patients with sepsis and ARDS, and it could play a pivotal role in kidney-lung crosstalk (50–53). Ang-2 is stored in Weibel-Palade bodies in endothelial cells and is released in response to endothelial activation (54). It acts in an autocrine manner as an antagonist for the Tie-2 receptor, which is predominantly expressed by endothelial cells to promote vascular leakage, and it is opposed by the agonistic action of angiopoietin-1 (55). As a biomarker, polymorphisms in the *Ang-2* gene have been linked to increased risk of ARDS, and higher serum Ang-2 levels correlate with impaired oxygenation and an increased risk of mortality in patients with ARDS (13, 56, 57). The angiopoietin/Tie-2 signaling axis plays an important role in vascular development during nephrogenesis, and a study of renal transplant recipients demonstrated that renal ischemia/reperfusion injury leads to rapid release of Ang-2, suggesting that Ang-2 could contribute to the development of ARDS in patients with AKI (12, 58, 59).

LUNG MEDIATED KIDNEY INJURY

Available data support the concept of distant organ effects on the lungs in AKI caused by a complex interplay between multiple cellular and molecular modulators of the immune system, which can initiate and perpetuate damage to the lungs. This is all under the assumption that the initial site of injury is the kidneys, and it is important to recognize the bidirectionality of kidney-lung crosstalk. Despite the high incidence of AKI in patients with ARDS, the impact of ALI on this ARDS-AKI construct and the effects of mechanical ventilation on the kidneys are not well understood (1). The leading hypotheses of lung mediated AKI include the direct effects of hypoxemia and hypercarbia on renal blood flow and renal cell injury, the systemic inflammatory response, and other molecular mediators causing direct renal cell damage (**Table 2**).

Hypoxemia, Hypercapnia, and Tissue Hypoxia

ALI and ARDS often lead to hypoxemia and hypercapnia, both of which affect renal blood flow and can lead to direct renal ischemia and subsequent injury. While the hallmark of ARDS is hypoxemic respiratory failure, hypercapnia can result from either the primary disease process, lung protective strategies limiting ventilation, or frequently, a combination of the two. Specifically, the current recommendations for treatment of ARDS include targeting lung protective strategies with lower goals for oxygen levels (both partial pressure of arterial oxygen and systemic saturations) and permissive hypercapnia (60). Both hypoxemia and hypercarbia have significant effects on renal blood flow and potentially lead to the development and progression of AKI. The presence of severe hypoxemia (Pa02 $<$ 40) leads to decreased renal blood flow and renal dysfunction (60). There are conflicting reports regarding moderate or mild hypoxemia on renal blood flow. Some studies suggest acute hypoxemia, even at mildly low systemic oxygen saturation levels of 88%, causes an acute decrease in renal blood flow while others suggest there is a kidney-lung protective strategy with mild hypoxemia with an increase in urine output, called the hypoxemic diuretic response (68). The mechanisms of hypoxemic changes in renal vascular tone and blood flow are largely unknown but thought to be related to activation and/or inactivation of nitric oxide, angiotensin II, endothelin, bradykinin, and the sympathetic reflex (61, 68, 69). The exact threshold of hypoxemia that is no longer "protective" and, instead, becomes injurious to the renal tissue bed requires further delineation. Hypercarbia, in turn, leads to decreased renal blood flow and perhaps has a stronger impact than hypoxemia, especially in the acute setting (60, 69).

The arterial partial pressure of carbon dioxide is inversely related to renal blood flow in animal models and in subjects with normal respiratory physiology, acute respiratory failure, and chronic obstructive pulmonary disease. Hypercapnia directly causes renal vasoconstriction and systemic vasodilation inducing the release of noradrenaline and the activation of the renin-angiotensin-aldosterone system which also contributes to renal vascular tone (69). Decreased renal blood flow, in turn, leads to renal hypoxia, and apoptosis and necrosis with resultant vascular and tubular damage culminating in acute tubular injury (70). Highly metabolically active and energy dependent proximal tubular cells are most sensitive to hypoxic injury as the medulla becomes far more hypoxic than the renal cortex in states of decreased renal blood flow (71).

Inflammatory Mediators of Kidney Damage in the Setting of ARDS

An additional suggested mechanism of lung-kidney crosstalk involves extracellular nucleotides released by injured pulmonary epithelial cells. Nucleotides are molecules that modulate numerous functions including vascular tone, apoptosis, membranous ion conductance, and trans alveolar fluid regulation in the lungs. Nucleotides are released by pulmonary epithelial cells in response to physical stimuli including shear stress during mechanical ventilation. In addition, nucleotides induce the synthesis and release of cytokines, specifically IL-6, which is a proinflammatory mediator described in the pathogenesis of AKI and the generation of renal tubular injury (72, 73). Douillet et al. demonstrated that mechanical ventilation alters the nucleotide and purinoreceptor expression in the kidney, even in the presence of protective mechanical ventilation strategies, suggesting ongoing lung-kidney cross talk in the setting of lung injury and mechanical ventilation (63, 74).

Renal cell injury has also been suggested by Imai et al., who compared injurious and non-injurious ventilator strategies (4). Injurious ventilator strategies led to the production of inflammatory cytokines and chemokines IL-8, MCP-1, and GRO, all of which have been implicated in the pathophysiology of AKI (4, 75). Additionally, proximal tubular cell apoptosis was observed *in vitro* with elevated blood urea nitrogen and creatinine levels as well as *in vivo* in rabbit models with injurious ventilator strategies; hypothesized to be secondary to soluble Fas ligand (sFasL), an important mediator of renal cell injury via apoptosis (4). Lastly, nitric oxide, a vasodilator that has been shown to have systemic and renal cytotoxic effects, has been implicated in ARDS-AKI construct. Choi et al. showed that injurious mechanical ventilation induced nitric oxide synthase (NOS) expression in both the lung and kidney, causing release of vascular endothelial growth factor causing increased vascular permeability and cytokine release (76).

Mechanical Ventilation as a Pro-inflammatory state

In addition to direct effects of hypoxemia, tissue hypoxia, and hypercapnia, lung injury involves multiple cytokines, chemokine, and pro-inflammatory pathways leading to kidney specific injury and the development of AKI. Mechanical ventilation, especially when higher tidal volumes and mean airway pressure are used and lung protective principles are not applied, propagates lung injury through atelectotrauma and sheer stress and contributes significantly to the release of damage associated molecular patterns (DAMPs), and various cytokines, and chemokines (77). In fact, inflammatory cytokines in patients ventilated with lung protective strategy were significantly decreased compared to controls who received standard mechanical ventilation in randomized control trials, with a noted reduction in bronchoalveolar concentrations of polymorphonuclear cells, TNF-α, IL-1β, soluble TNF-α receptor, and IL-8 (64). Plasma and bronchoalveolar levels of IL-6, IL-8, soluble TNF-α receptor, and IL-1 receptor antagonist were also decreased, all of which have been implicated in the pathophysiology of AKI (64, 65). It is reasonable to surmise that even in the absence of a primary pulmonary pathology, injurious ventilation strategies could contribute to the organ crosstalk, leading to remote organ injury manifested as AKI (65). Receptor for Advanced Glycation End Products (RAGE) is considered an alveolar epithelial injury marker and levels can increase in the serum within an hour after a recruitment maneuver, which is typically characterized by brief but sustained increase in airway pressure in order to recruit collapsed segments of injured lung (78). Certain subgroups of adult ARDS patients have higher RAGE levels, suggesting more epithelial damage (79, 80). Soluble forms of these mediators spill over into circulation and are measurable in peripheral blood, an example that many other DAMPs contribute to remote signaling and inflammation propagation in ARDS (66).

Most recently, the changing epidemiology of AKI among the pandemic SARS-CoV-2 related ARDS cases worldwide has further highlighted the potential mechanistic link between a therapeutic approach and remote organ injury propagation. Many centers have reported a high incidence of renal replacement therapy requiring AKI in the setting of COVID-19 early on in the pandemic with dismal outcomes (81). The use of higher end pressures has been associated with AKI (62). Others have proposed that aggressive fluid restriction and attempt at decongestion through liberal diuretic use has exacerbated kidney injury and delayed renal recovery, leading to worsening of AKI and earlier use of RRT (82). The high incidence of AKI in patients with COVID-19 underscores dynamic interplay between the kidneys and the lungs.

Although our understanding remains incomplete, awareness of continuous interaction and organ crosstalk highlights the importance of vigilance related to lung protective ventilation strategies in the management of ARDS in order to limit lung mediated remote organ injury, such as AKI. In addition to inflammatory consequences, mechanical ventilation has a number of hemodynamic effects and influences neurohormonal factors that contribute to AKI. Elevated pulmonary vascular resistance and right ventricular strain in the setting of ARDS might impact renal perfusion (74). Elevated filling pressures contribute to decreased renal perfusion, especially in the setting of marginal arterial pressures, which can initiate and propagate AKI. In addition, mechanical ventilation can alter

TABLE 3 | Future basic and translational research directions in kidney-lung crosstalk.

- Further elucidation of the molecular and cellular basis of organ crosstalk
- Determination of ventilator and hemodynamic parameters that optimize renal perfusion in patients with ARDS
- Development of alternatives to animal models for studying organ crosstalk, such as organoid-based microfluidic chips
- Application of systems biology tools such as transcriptomics, proteomics, metabolomics, and single cell sequencing to identify molecular phenotypes of pediatric AKI and ARDS
- Incorporation of molecular phenotyping into future clinical trial design

renal hemodynamics by increasing sympathetic tone and renin-angiotensin aldosterone system activation (83–85).

Fluid Overload, ARDS Phenotypes and AKI

Knowledge of the pathophysiologic links between AKI and ARDS could be leveraged to identify patients with AKI who are at risk of developing ARDS and can be used to develop targeted therapies that prevent or treat this complication. Unfortunately, the complex interplay between both organ systems discussed thus far makes this endeavor less attainable in clinical practice. Lung protective mechanical ventilation and fluid management to restore effective arterial blood volume are the cornerstones of ARDS management. Currently, avoiding positive fluid balance remains the most important predictor of pulmonary complications in patients with AKI and is the primary target for intervention. Restrictive fluid management in ARDS has indeed become the standard of care (86, 87). Despite advances in medical care, treatment options remain limited and are largely supportive. Lack of positive data from multiple interventional randomized control trials has incited a search towards discerning molecular sub-phenotypes of ARDS based on clinical and biological determinants. Recent work aimed at understanding the different presentations clustered under the rather heterogeneous complex syndromic designation of ARDS has provided fascinating insight regarding patient and disease specific characteristics of ARDS and differential response to treatment that drive this complex construct.

Calfee et al. have described two different subphenotypes ARDS in patient cohorts enrolled in two randomized controlled trials based on clinical and biomarker variables derived from latent class analysis (1, 67). Importantly, both subphenotype classifications relied on the plasma biomarkers not available in routine clinical practice to delineate the two groups, signifying that these specific biomarkers may be uncovering aspects of underlying pathophysiology not captured by routine clinical variables. In these analyses, the inflammatory subphenotype 2 had higher levels of proinflammatory biomarkers such as IL-8, IL-6, and sTNF receptor 1, and higher plasma levels of and RAGE compared to subphenotype 1. Subjects with sepsis associated ARDS were more likely to belong to subphenotype 2 compared to subjects with trauma associated ARDS who were classified as subphenotype 1. Subjects with phenotype 2 were more likely to have higher mortality, and fewer organ failure free and ventilator free days. Most surprisingly, the two groups had differential response to treatment strategies: subjects in subphenotype 1 had higher mortality with higher versus lower PEEP; conversely, in subphenotype 2 higher PEEP was associated with lower mortality. Even more pertinent to our topic, the two subphenotypes had a differential response to fluid exposure; subphenotype 2 had a higher mortality when assigned to liberal fluid management strategy. Conversely, subphenotype 1 had a higher mortality with restrictive fluid management. The underlying reason for this differential response remains speculative. However, higher Ang-2 levels in subphenotype 2 signal endothelial damage, putting patients at risk of altered fluid excretion and fluid imbalance leading to fluid overload and higher mortality. Conversely, fluid restriction in patients sub phenotype 1 with lower Ang-2 levels could signify lower effective arterial blood volume and impaired end organ perfusion and higher mortality (5). Although subjects in subphenotype 2 had fewer ventilator free days compared to subphenotype 1, there was no association with fluid management strategy, perhaps signaling the contribution of other extra pulmonary organ injury such as AKI leading to fluid overload and worse pulmonary compliance. Interestingly, none of the extensive clinical variables tested was predictive of a subphenotype, suggesting that targeting clinically relevant subphenotypes might be the next strategy in designing interventional trials.

It is easy to speculate that pediatric AKI could very well represent a heterogenous syndrome with varied responses to fluid exposure significantly impacting lung-kidney interactions. Stratified analysis of a prospective study showed that mortality was associated with greater cumulative fluid balance on Day 3 of ARDS with concomitant AKI (88). In addition, higher degrees of inflammation, indicated by elevated IL-6 levels on day 1 were associated with positive cumulative fluid balance, AKI and, hence, mortality. Conceivably, higher IL-6 levels could signal a hyperinflammatory subphenotype of ARDS that might result in increased vascular permeability, endothelial damage, and AKI. Currently available data do not differentiate between adverse effects noted on the two subphenotypes of ARDS and the concomitant or sequential occurrence of oliguric vs. non-oliguric AKI. Oliguric AKI is known to carry a worse prognosis compared to non-oliguric AKI, yet available pediatric data are conflicting regarding oliguric AKI as a precursor to development of fluid overload (14, 89–93). Higher levels of inflammatory and endothelial activation mediators in the inflammatory subphenotype could result in microcirculatory dysfunction and energy failure leading to impaired fluid excretion, contributing to fluid overload and, hence, worse pulmonary compliance. Currently available adult data revealing the paradoxical response to fluid exposure suggest that the hyperinflammatory subphenotype could be the target population to test whether restrictive fluid strategy would help mitigate the effects of endothelial damage and vascular permeability, and related higher risk of fluid overload and AKI in this population. To help advance our understanding of the complex mechanisms involved in ARDS, AKI, and their interactions, it is crucial to identify if similar subphenotypes also exist in pediatric ARDS in order

to develop and test an individualized approach to clinical management, specifically pertaining to ventilator and fluid exposure, to care for our patients with a more informed and personalized approach.

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Critical illness is largely a state of organ crosstalk and interaction; therefore, successful management requires a thorough understanding of its management. Changing epidemiology of pediatric AKI has clearly placed this syndrome in the setting of multiple organ dysfunction especially as it relates to the most severe forms of AKI with the poorest outcomes. Similarly, refinement of the pediatric ARDS definition has improved our understanding of the disease pathophysiology. As such, pediatric AKI and ARDS are the two most common organ failures intensivists deal with on a daily basis. Recent evidence, especially around mechanistic pathways in each syndrome, has enhanced our appreciation of the actual scale of organ crosstalk that extends beyond simply fluid accumulation and its management in AKI and ARDS. Multiple disease-specific molecular mediators and inflammatory pathways are involved in organ crosstalk in the AKI-ARDS construct, and the reciprocal hemodynamic effects of elevated pulmonary vascular resistance and central venous pressure (CVP) augment both renal and pulmonary congestion and impair renal oxygenation. Future research (**Table 3**) should be directed at further elucidating the molecular and cellular basis of kidney lung crosstalk, which will require the development of alternatives to animal models. Potentials strategies include systems biology applications such as "–omics" platforms and single cell sequencing of circulating immune cells, as well as the development of microfluidic organ-on-a-chip models that incorporate lung and kidney organoids to model organ crosstalk. Knowledge gained from these studies could be used to develop targeted therapies and molecular phenotyping tools that identify discrete subtypes of pediatric AKI and ARDS. Ultimately, this knowledge could arm clinicians with the tools for a precision medicine based approach, such as biomarker directed fluid management and other therapies. While it will be some time before these ambitious goals are realized, in the interim, clinicians must develop an appreciation of complexity of organ interactions and maintain vigilance regarding bidirectionality while treating these interrelated conditions in the critically ill pediatric patient.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REVIEW
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A Review on the Application and Limitations of Administrative Health Care Data for the Study of Acute Kidney Injury Epidemiology and Outcomes in Children

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Administrative health care databases contain valuable patient information generated by health care encounters. These "big data" repositories have been increasingly used in epidemiological health research internationally in recent years as they are easily accessible and cost-efficient and cover large populations for long periods. Despite these beneficial characteristics, it is also important to consider the limitations that administrative health research presents, such as issues related to data incompleteness and the limited sensitivity of the variables. These barriers potentially lead to unwanted biases and pose threats to the validity of the research being conducted. In this review, we discuss the effectiveness of health administrative data in understanding the epidemiology of and outcomes after acute kidney injury (AKI) among adults and children. In addition, we describe various validation studies of AKI diagnostic or procedural codes among adults and children. These studies reveal challenges of AKI research using administrative data and the lack of this type of research in children and other subpopulations. Additional pediatric-specific validation studies of administrative health data are needed to promote higher volume and increased validity of this type of research in pediatric AKI, to elucidate the large-scale epidemiology and patient and health systems impacts of AKI in children, and to devise and monitor programs to improve clinical outcomes and process of care.

Keywords: administrative health care data, acute kidney injury, nephrology, epidemiology, pediatrics

INTRODUCTION

Acute kidney injury (AKI), characterized by an abrupt deterioration of kidney function, is common in adults and children, and the incidence is increasing (1). The Kidney Disease Improving Global Outcomes (KDIGO) definition incorporates rise in serum creatinine and decreased urine output to identify AKI and classify severity. Approximately 5% of hospitalized children develop AKI (2), and 20–50% of children in the intensive care unit (ICU) and those with cardiac surgery develop AKI (3, 4). Pediatric and adult AKIs are associated with adverse in-hospital outcomes, including

mortality and prolonged hospitalization. Many studies among adults have shown that AKI is a strong risk factor for chronic kidney disease (CKD), end-stage kidney disease (ESKD), hypertension (HTN), cardiovascular disease, and mortality (5). Among children, available data suggest that AKI is also associated with worse long-term outcomes (6–9).

Administrative health care databases have enabled expansive observational studies because these data are pre-collected and easily accessible and provide a wealth of information regarding epidemiology, risk factors, and outcomes of AKI (10). The purpose of this review is to provide an overview of administrative health care data, as well as its strengths and limitations. In addition, we review validation studies to identify individuals with AKI using administrative health data. Finally, we provide an update on the incidence, risk factors, and outcomes after AKI, as learned from the studies conducted in the last 5 years using administrative health data.

ADMINISTRATIVE HEALTH CARE DATA RESEARCH

Administrative health care databases store large quantities of information that are routinely compiled and updated by provinces and/or countries on patients, health care providers, and institutions during various patient encounters (11, 12). Examples of data collected are summarized in **Figure 1** and include physician billing codes, prescription claims, vital records, and hospitalization/discharge summaries (13). These data contained within the administrative health databases are often referred to as "big data," which are distinguished by the large volume of information, speed at which it is generated, and the wide range of fields that it covers (14). Epidemiological studies, in particular, benefit greatly from the availability of administrative health care databases to evaluate and track the health of large populations over a period (12). For example, the *International Classification of Diseases* (*ICD*) diagnostic codes found in the databases have been established as an international standard for classification of diseases (15, 16). Using standardized *ICD* diagnostic codes as a main source of data allows clinical epidemiologists to study patterns of disease, patient care, and various health outcomes in an efficient way (17).

In recent years, the use of administrative health data as a powerful research tool has become increasingly established and extensively applied to various fields of epidemiological research (11, 15, 16). AKI, in particular, is an ideal disease to study using administrative health data (18) due to the high prevalence in hospitalized patients, increased risk for major morbidity (CKD, progression to ESKD, and death), financial costs, and recent research demonstrating that care of patients with AKI is suboptimal due to avoidable systemic issues (18). A series of statements from the Acute Dialysis Quality Initiative (ADQI) consensus conference in 2015 outline the potential of large database research for AKI, including real-time prediction of risk for AKI, developing electronic alerts for quality improvement, and "tagging" AKI patients for longitudinal care and advancing our understanding of long-term outcomes following AKI (18–23). Currently, real-time AKI alerts using electronic systems notify health care providers using the KDIGO definition of AKI events (20). In the future, however, machine learning could incorporate real-time patient comorbidities, nephrotoxin exposure, and so on that would allow these electronic systems to provide prognostic data directly to health care providers managing the individual patient, even before an AKI event has occurred (20). The potential real-time application of "big data" to the management of AKI at the individual, organizational, and institutional level is summarized in **Figure 2**.

STRENGTHS AND LIMITATIONS OF ADMINISTRATIVE HEALTH DATA RESEARCH

To effectively conduct and interpret outcomes of administrative health data research, it is important to understand the strengths and limitations (**Table 1**).

Strengths

One of the most significant advantages of administrative health care data is the very large sample size, which in turn reduces sampling error, increases statistical power, and increases validity (16, 24). The inclusion of a larger and more diverse population also increases generalizability of the study findings to a greater population (25). Having larger numbers of variables collected also allows researchers adjust for many types of variables in multivariable analyses (24).

Although prospective randomized controlled trials (RCTs) are considered to be the gold standard of scientific evidence in clinical medicine, it is often difficult to conduct them because of various logistical, financial, and ethical limitations (24). As administrative health care data are pre-collected and readily available, they allow studies to be less costly and much quicker to perform (24). In fact, cluster RCTs that obtain data through administrative health databases can act as a solution to allow for inclusion of a broad number of facilities and larger representative samples of patients (26). As with any cluster RCT, care would be required to ensure information about exposure status, and outcomes are generalizable and derived from data sources in a consistent manner across trial centers. The heterogeneity and accessibility of administrative health data also allow for easier identification of patients with rare diseases (27–29).

Administrative health care databases often allow patients to be followed over extended time periods (6, 30, 31). Unlike studies that require primary data collection, administrative health databases do not involve researchers having to contact individuals, and loss to follow-up is not a significant issue (unless the patients do not immigrate) when conducting longitudinal studies for outcomes. In fact, researchers can follow patients over a long period by linking their clinical research records to administrative databases with the patients' consent (32). This, in turn, simplifies the follow-up process and eliminates any chances of non-response and recall bias (33).

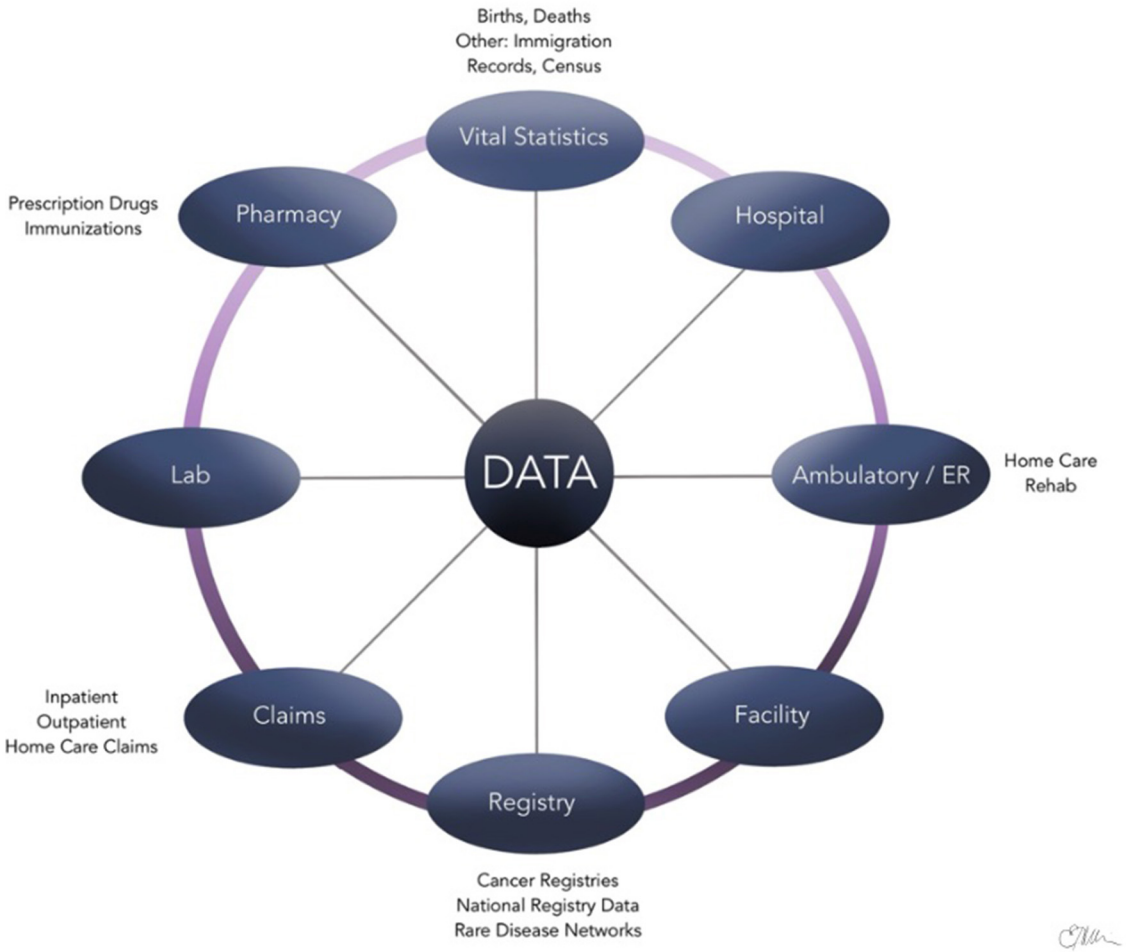

FIGURE 1 | Sources of administrative health data.

Administrative health care data also can be supplemented and linked with other data sources, allowing for a larger and more comprehensive data set. This involves the easily computerized process of linking an individual using personal identifier variables across different databases without affecting patient privacy (16). Other data sources, such as census or citizenship data, allow researchers to gain more information about certain target groups' socioeconomic status and lifestyle (34, 35). Linkage with electronic medical records, which includes more detailed information about a patient's health, helps to increase the validity of research findings (36, 37).

Limitations

Because of health care databases being structured primarily for administrative and billing purposes, they often lack additional clinical information about the diseases of interest, health outcomes, and medications (38). Detailed data about some comorbidities, anthropometric measures, quality of life, education status, physical activity levels, and patient-reported outcomes are usually unavailable or recorded inconsistently and can negatively impact the research process (39–41). Additionally, changes in clinical diagnostic billing coding practices and different software systems that different physicians and institutions use may cause additional gaps in data (41). For example, the mandatory transition from *ICD-9* to *ICD-10* diagnostic codes in 2015 involved nearly four times more codes (42). Hence, it is important to consider the changing thresholds and other factors for diagnosing certain diseases to prevent overestimation or underestimation of cases when evaluating incidence and outcomes, which is mainly accomplished through regular and rigorous validation studies. To address this, it is essential for policymakers to devise a standard framework surrounding the coding and software system used within institutions to help bridge the data and communication gaps. This will help ensure that the collection of data is more consistent within and between countries and that the information can be used more effectively in research studies.

Patient identification in administrative health data research is usually made upon the basis of specific diagnostic or procedural codes of disease (11). Validation studies that evaluate the different

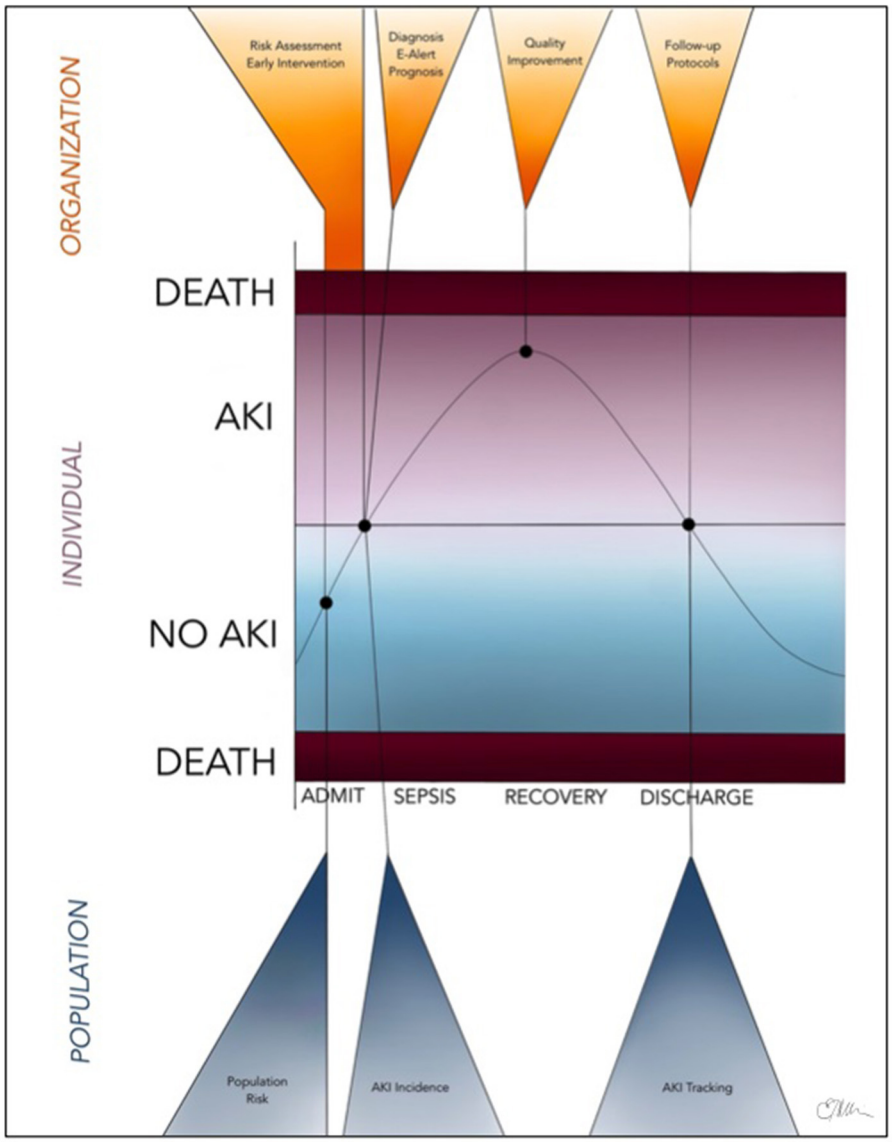

FIGURE 2 | Future, real-time application of "big data" (including administrative health data and electronic medical records) to the identification, management, and monitoring of children and adults with AKI at the individual, organizational, and population levels.

combination of codes and criteria, also known as "algorithms," are essential when conducting administrative health research, but are currently very limited (11, 43). A scoping review for validation studies of administrative health data from 2014 was able to identify only a very limited number of pediatric validation studies for a wide range of diseases and revealed that most studies focused exclusively on adult populations (44).

When working with larger sample sizes in administrative data research, issues related to statistical analyses may occur. For instance, although associations between outcome variables and exposures present as statistically significant ($p < 0.05$) due to a large sample size and power, clinical significance is not always evident and should be critically evaluated when reviewing the results (25). The clustered nature of the data sets in administrative health databases may also result in overestimating associations, which may lead to incorrect conclusions, and ideally should be addressed through models that take into account the hierarchical nature of data present (11).

Just like any other type of study, administrative health data research has the potential to be affected by information bias. Misclassification of an outcome can result when there is unclear or unavailable clinical documentation or a range of definitions for a certain disease, as mentioned previously (16). To address this, adding additional data sources through data linkage can be performed (16). Confounding by indication (also known as indication bias) commonly occurs when people with certain

TABLE 1 | Summary of strengths and limitations of administrative health research.

Strengths	Limitations
Large sample size	**Gaps in clinical information**
• Reduces sample error and biases • Provides information for addressing precise clinical research questions	• Lack of information about certain comorbidities and confounders • Changes to coding practices contribute to gaps in data
Accessibility of data	**Lack of validation studies**
• Addresses drawbacks of traditional RCTs • Cost-effective • Increasingly accessible by the broader research community • Ability to study rare diseases	• Gaps in literature for validation studies of administrative health data • Pediatric-focused validation studies are very limited
Long follow-up	**Statistical issues and biases**
• Continuous and long periods of data collection • Easy follow-up process	• Overestimated statistical significance • Information/misclassification bias • Selection bias • More expertise in analysis of administrative health databases required
Ability to link data to other data sources	
• Other databases • Electronic medical records • Census and surveys	

conditions are more likely to get certain tests or diagnoses attributed to them (45). For example, if someone already has AKI, they may be more likely to be diagnosed with CKD, but this does not necessarily mean they were originally at a higher risk for having CKD.

Additionally, selection bias may result when certain diagnostic codes do not selectively represent a condition under study as study samples will be restricted to a special population, especially when consent is required (11). Careful planning of studies should be done to avoid these biases. When carrying out different objectives during an administrative health data–based research study, using a multidisciplinary team of researchers that include statisticians with expertise in health data analysis and modeling of the specific database being used is essential (11, 39).

VALIDATION STUDIES FOR ADMINISTRATIVE HEALTH CARE DATA IN AKI

Since the late 1990s, there has been increasing interest in validating the use of discharge and procedural billing codes from administrative health care data research on AKI, including severe AKI requiring kidney replacement therapy (KRT) (46). In 2011, Vlasschaert et al. published a systematic review on the validity of using administrative codes for AKI and CKD (47). The results of this review showed high specificity but lower sensitivity for identifying AKI using administrative data; of note, sensitivity is improved when administrative health care data are used to identify more severe AKI and/or AKI treated with KRT. We conducted a MEDLINE search with the following search terms: (1) *acute kidney injury, aki, acute renal failure,* or *continuous renal replacement therapy*, and (2) *admin* adj3 data** to identify validation studies published since this systematic review, which identified an additional eight studies. A summary of the results of these studies (48–55) and a selection of those published in the systematic review (56–61) are included in **Table 2**. To our knowledge, this represents the most up-to-date summary of validation studies for AKI administrative health research.

We have summarized 14 studies that took place between 2004 and 2020. Validation studies have generally compared cases of AKI identified from administrative data, including diagnostic and/or procedure codes for AKI, to a reference standard. More recent validation studies tended to use *ICD-10* codes (50, 52, 55, 59), although many studies utilized *ICD-9* codes (51, 53, 54, 56–61). For the most part, the reference standard has consisted of either standardized chart review (48, 50–53, 56, 57, 59) or laboratory data linked to either an (1) electronic health record (49, 51) or (2) administrative database containing data from inpatient and outpatient laboratories (54, 55, 58, 60, 61). The source for the reference standard significantly impacted study size with full chart reviews tending to have much smaller study populations. Early studies used acute renal failure (ARF) (56–61) for the reference standard, but the definition of ARF was not always well-defined. Newer studies have tended toward using KDIGO criteria (62) for AKI using serum creatinine levels as the reference standard (50, 51, 53); two studies used serum creatinine or urine output criteria (51, 53). Several studies compared only patients with more severe AKI against the reference standard (48, 51, 53, 55). Most studies were done in hospitalized adults (48, 50–52, 54–61); two studies examined adults admitted to the ICU (48, 55), and two early studies examined adults post–coronary artery bypass graft (58) operation and post–acute myocardial infarction (59). Only two studies were done in children (49, 53); one study examined hospitalized pediatric patients exposed to nephrotoxins (49) and the other examined pediatric patients admitted to the ICU (53).

Most studies reported various parameters, such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the administrative data vs. reference data for identifying cases of AKI or ARF. Specificity of administrative data tended to be high (86.7–100%). Studies comparing administrative data to a standardized chart review, regardless of definition used, had a high specificity (≥94%) (48–53, 56, 57, 59–61). Two studies compared administrative data to another administrative database and reported reduced specificity (86.7–98.3%); however, these results are likely to be impacted by the quality of data in the administrative database used as a reference standard and are less reliable. However, sensitivity tended to be highly variable (5.9–94.5%). Studies with higher severity of AKI or AKI receiving KRT or ARF generally reported a higher sensitivity. When compared to standardized chart review as the reference standard (51, 53), administrative data identified patients with stage 3 AKI by KDIGO criteria with a sensitivity of 36.5% in hospitalized adults (51), 14.3% in pediatric cardiac surgery patients in ICU (53), and 42.2% for pediatric non-cardiac surgery patients in ICU (53). In one study of billing codes of adult hospitalizations, applying criteria for creatinine or urine output

TABLE 2 | Summary of validation studies for acute kidney injury and renal replacement therapy codes in adults and pediatric administrative health research.

References	Validated Measure	Study Population	N	Administrative Health Data Source	Reference Standard	Study Findings	Limitations
Quan et al. (56)	ARF	Adults hospitalized in Canada in 1996–1997	1,200 (600 medical service, 600 general surgical service)	Discharge billing codes, including ICD-9 diagnostic codes for ARF	Standardized review of medical charts for ARF	**Sensitivity-% (CI)** / **Specificity-% (CI)** / **PPV-% (CI)** / **NPV-% (CI)** ARF: 33.3 (CI NR) / 99.1 (CI NR) / 15.4 (CI NR) / 99.7 (CI NR)	- Small sample size may limit generalizability - Reference standard definition of ARF is unclear - Cohort admitted in 1996–1997; higher sensitivity may be apparent based on more current practices and increased AKI awareness
Liangos et al. (57)	ARF	Adults without ESRD hospitalized in USA in 2001	13,237	NHDS administrative database, which provides discharge billing codes, including ICD-9 diagnostic and procedure codes for ARF	Standardized review of medical charts with ARF defined using variable change (104, 105)	**Sensitivity-% (CI)** / **Specificity-% (CI)** / **PPV-% (CI)** / **NPV-% (CI)** ARF: 19.2 (CI NR) / 99.6 (CI NR) / 87.6 (CI NR) / 90.1 (CI NR)	- Cohort admitted in 2001; higher sensitivity may be apparent based on more current practices and increased AKI awareness - Validation study done in single tertiary centre, which may limit generalizability
Parker et al. (58)	ARF	Adults hospitalized for CABG in USA from 2000 to 2001	38,230	Discharge billing codes using ICD-9 diagnostic codes for ARF	CABG Mortality Reporting Program, which provides clinical registry data, including complications	**Sensitivity-% (CI)** / **Specificity-% (CI)** / **PPV-% (CI)** / **NPV-% (CI)** ARF: 22.4 (CI NR) / 98.3 (CI NR) / 31.7 (CI NR) / 97.3 (CI NR)	- CABG cohort may limit generalizability - Absence of a "gold standard," Reference standard did not use chart reviewed data and definition of ARF is unclear - Cohort admitted in 2000–2001; higher sensitivity may be apparent based on more current practices and increased AKI awareness

(Continued)

TABLE 2 | Continued

<table>
<tr><th>References</th><th>Validated Measure</th><th>Study Population</th><th>N</th><th>Administrative Health Data Source</th><th>Reference Standard</th><th>Study Findings</th><th>Limitations</th></tr>
<tr><td>So et al. (59)</td><td>ARF</td><td>Adults hospitalized with AMI in Canada from 1994 to 2004</td><td>193</td><td>Discharge billing codes using either ICD-9 (from 1994 to 2000) and ICD-10 (from 2001 to 2004) diagnostic and procedure codes for ARF</td><td>Standardized review of medical charts for ARF</td><td>
<table>
<tr><th></th><th>Sensitivity-% (CI)</th><th>Specificity-% (CI)</th><th>PPV-% (CI)</th><th>NPV-% (CI)</th></tr>
<tr><td>ARF (ICD-10, 2001–2004)</td><td>80.0 (51.91–95.67)</td><td>95.5 (91.34–98.04)</td><td>60.0 (36.05–80.88)</td><td>98.3 (95.02–99.64)</td></tr>
<tr><td>ARF (ICD-9, 1994–2000)</td><td>80.0 (51.91–95.67)</td><td>98.3 (95.15–99.65)</td><td>80.0 (51.91–95.67)</td><td>98.3 (95.15–99.65)</td></tr>
</table>
</td><td>- Small sample size, cohort with AMI may limit generalizability
- Reference standard was collected in a different province and definition of ARF is unclear
- Cohort admitted in 1994–2004; higher sensitivity may be apparent based on more current practices and increased AKI awareness</td></tr>
<tr><td>Waikar et al. (60)</td><td>ARF</td><td>Adults hospitalized in USA in 1994 and 2002</td><td>26,751 admissions (19,206 in 2002; 7,545 in 1994)</td><td>NIS administrative database, which provides discharge billing codes, including ICD-9 diagnostic and procedure codes for ARF</td><td>Linked laboratory and hospital administrative data with ARF defined as 100% increase between nadir and peak SCr</td><td>
<table>
<tr><th></th><th>Sensitivity-% (CI)</th><th>Specificity-% (CI)</th><th>PPV-% (CI)</th><th>NPV-% (CI)</th></tr>
<tr><td>ARF (2002)</td><td>29.3 (CI NR)</td><td>97.4 (CI NR)</td><td>59.1 (CI NR)</td><td>91.5 (CI NR)</td></tr>
<tr><td>ARF (1994)</td><td>17.4 (CI NR)</td><td>98.7 (CI NR)</td><td>63.5 (CI NR)</td><td>89.9 (CI NR)</td></tr>
</table>
</td><td>- Reference standard based on laboratory data may have resulted in misclassification of ARF as diagnostic standard
- Cohort admitted in 1994 and 2002; higher sensitivity may be apparent based on more current practices and increased AKI awareness
- Validation study done in two academic centres, which may limit generalizability</td></tr>
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TABLE 2 | Continued

References	Validated Measure	Study Population	N	Administrative Health Data Source	Reference Standard	Study Findings	Limitations
Waikar et al. (61)	ARF	Adults hospitalized in USA in 2004	99,629	Discharge billing codes, including ICD-9 diagnostic and procedure codes for ARF	Linked laboratory and hospital administrative data with ARF defined using nadir and peak SCr: (1) 100% change and (2) a variable change (104, 105); standardized review of 300 charts for ARF requiring dialysis	**Sensitivity-% (CI)** / **Specificity-% (CI)** / **PPV-% (CI)** / **NPV-% (CI)** ARF [by Variable Change (104, 105)]: 28.3 (CI NR) / 99.0 (CI NR) / 80.2 (CI NR) / 91.0 (CI NR) ARF (Requiring Dialysis): 90.4 (CI NR) / 93.8 (CI NR) / 94.0 (CI NR) / 90.0 (CI NR) ARF (by 100% Change): 35.4 (CI NR) / 97.7 (CI NR) / 47.9 (CI NR) / 96.1 (CI NR)	- Reference standard based on laboratory data may have resulted in misclassification of ARF as diagnostic standard - Sampling strategy for chart review of ARF requiring dialysis may overestimate sensitivity
Blichert-Hansen et al. (48)	AKI-RRT	Adults admitted to ICU in Denmark between 2005 and 2010	50	Danish National Patient Registry, which includes discharge procedure codes for AKI-RRT	Standardized review of medical charts for ARF-RRT, including acute HD or CRRT	**Sensitivity-% (CI)** / **Specificity-% (CI)** / **PPV-% (CI)** / **NPV-% (CI)** AKI-RRT: NR / NR / 98 (91.0–99.8) / NR	- Small sample size limits generalizability - Study limited to AKI-RRT only - Sensitivity, specificity, and NPV could not be reported
Schaffzin et al. (49)	AKI	Children hospitalized in USA, exposed to 3+ nephrotoxins at once OR 3+ days of aminoglycoside therapy from 2011 to 2012	747 from retrospective cohort; 261 from prior prospective cohort (106)	Pediatric Health Information System, which includes medication and discharge billing codes for AKI	Standardized review of medical charts, merged with electronic medical record, using pRIFLE definition (using SCr criteria for R, I, and F strata)	**Sensitivity-% (CI)** / **Specificity-% (CI)** / **PPV-% (CI)** / **NPV-% (CI)** AKI (using retrospective cohort): 23.2 (14.0–32.2) / 95.0 (93.1–96.6) / 36.5 (23.6–51.0) / 90.9 (88.6–93.0) AKI [using prospective cohort (106)]: 21.4 (11.8–31.0) / 94.2 (90.1–97.5) / 57.7 (38.7–76.7) / 76.6 (71.2–82.0)	- Small sample size, single-center data may limit generalizability - pRIFLE criteria may still underestimate nephrotoxin-associated AKI without daily screening, as in the prospective cohort

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TABLE 2 | Continued

References	Validated Measure	Study Population	N	Administrative Health Data Source	Reference Standard	Study Findings	Limitations
Tomlinson et al. (50)	AKI	Adults without ESRD hospitalized in England in 2005 and 2010	121 (58 in 2005, 63 in 2010)	Discharge billing codes, including ICD-10 diagnostic code for AKI	Standardized review of selected medical charts using KDIGO AKI definition (using SCr criteria)	**Sensitivity-% (CI)** / **Specificity-% (CI)** / **PPV-% (CI)** / **NPV-% (CI)** AKI: NR / NR / 95 (91–99) / NR AKI, 2005 Only: NR / NR / 95 (89–100) / NR AKI, 2010 Only: NR / NR / 94 (88–100) / NR	- Small sample size, single-center data may limit generalizability - One diagnostic code examined only - Sensitivity, specificity, and NPV could not be reported
Grams et al. (51)	AKI	Adults without ESRD hospitalized in the US between 1996 and 2008, Atherosclerosis Risk in Communities (ARIC) study participants	10,056	Discharge billing codes, including ICD-9 diagnostic and procedure codes for AKI	Standardized review of selected medical charts using KDIGO AKI definition (using SCr criteria) Standardized review of electronic medical record using KDIGO AKI definition (using SCr or UO criteria)	**Sensitivity-% (CI)** / **Specificity-% (CI)** / **PPV-% (CI)** / **NPV-% (CI)** AKI (vs. Chart Review): 17.4 (11.6–23.1) / 99.6 (99.3–99.9) / 92.0 (85.9–98.2) / 81.8 (76.5–87.2) Stage 2 or 3 AKI (vs. Chart Review): 40.3 (CI NR) / NR / NR / 99.9 (CI NR) Stage 3 AKI (vs. Chart Review): 36.5 (CI NR) / 99.9 (CI NR) / NR / NR AKI (vs. Electronic Medical Record): 11.7 (8.8–14.5) / 98.9 (98.2–99.5) / 83.5 (75.4–91.7) / 69.3 (66.9–71.7)	- Cohort admitted between 1996 and 2008; nearly 50% of hospitalizations used for chart review were between 1996 and 2002. Sensitivity significantly increased when comparing hospitalizations between 1996 and 2002 vs. 2002 and 2008; age <65 vs. ≥65 years. This may reflect increased AKI awareness - Electronic medical record data is from one center, which may limit generalizability

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TABLE 2 | Continued

References	Validated Measure	Study Population	N	Administrative Health Data Source	Reference Standard	Study Findings	Limitations
Maass et al. (52)	ARF	Adults, aged 65 years or older, hospitalized in Germany between May-December 2010	3000 (of which 1500 were post-operative)	Discharge billing codes, including ICD-10 diagnostic and procedure codes for ARF	Standardized review of selected medical charts for ARF	**Sensitivity-% (CI)**: 17.6 (12.7–24.1); **Specificity-% (CI)**: 99.2 (98.7–99.4); **PPV-% (CI)**: 56.6 (CI NR); **NPV-% (CI)**: NR	- KDIGO criteria not applied
D'Arienzo et al. (53)	AKI	Children (aged 0–18 years) without ESRD admitted to pediatric ICU in Canada between 2003 and 2005	2051 (355 cardiac surgery, 1696 non-cardiac surgery)	Provincial health care administrative database using ICD-9 primary and secondary diagnostic and dialysis procedure codes	Standardized chart review using KDIGO AKI definition (using SCr or UO criteria) and severity	**Cardiac Surgery, Any AKI**: Sensitivity-% (CI) 5.9 (4.7–7.6); Specificity-% (CI) 100 (99.2–100); PPV-% (CI) 100 (88.2–100); NPV-% (CI) 49.4 (47.5–51.4) **Cardiac Surgery, Stage 2 or Worse AKI**: Sensitivity-% (CI) 14.1 (10.8–18.2); Specificity-% (CI) 99.3 (98.7–99.7); PPV-% (CI) 81.8 (67.4–91.2); NPV-% (CI) 84.0 (82.5–85.4) **Cardiac Surgery, Stage 3 AKI**: Sensitivity-% (CI) 14.3 (9.7–20.5); Specificity-% (CI) 98.1 (97.3–98.7); PPV-% (CI) 45.5 (31.7–59.8); NPV-% (CI) 91.3 (90.0–92.4) **Non-Cardiac, Any AKI**: Sensitivity-% (CI) 13.8 (12.6–15.1); Specificity-% (CI) 99.1 (98.9–99.3); PPV-% (CI) 82.4 (78.2–85.8); NPV-% (CI) 78.5 (77.8–79.2) **Non-Cardiac, Stage 2 or Worse AKI**: Sensitivity-% (CI) 23.6 (21.3–26.1); Specificity-% (CI) 98.3 (98.0–98.5); PPV-% (CI) 61.8 (57.0–66.3); NPV-% (CI) 91.7 (91.1–92.1) **Non-Cardiac, Stage 3 AKI**: Sensitivity-% (CI) 42.2 (38.0–46.5); Specificity-% (CI) 98.0 (97.7–98.2); PPV-% (CI) 51.5 (46.7–56.2); NPV-% (CI) 97.1 (96.7–97.3)	- Small sample size for cardiac surgery cohort - Center-specific practices may limit generalizability - Cohort admitted between 2003 and 2005; higher sensitivity may be apparent based on more current practices and increased AKI awareness
Etzioni et al. (54)	ARF	Adults hospitalized for surgical operations across 8 hospitals in USA between 2013 and 2015	41,432 surgical hospitalizations (37% general surgery, 20% orthopedic)	Intra-hospital administrative data using ICD-9 codes diagnostic and dialysis procedure codes	ACS' NSQIP administrative data, including patient information, treatment, and complications	Concordance (Cohen Kappa value) between administrative and ACS NSQIP data for ARF: 0.10. Hospital-specific concordance was not statistically significant ($P = 0.19$), suggestive of significant inter-hospital heterogeneity for ARF	- Absence of a "gold standard," Reference standard did not use chart reviewed data and confirm AKI using SCr or UO data - Significant inter-hospital variability is likely contributory to poor concordance

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TABLE 2 | Continued

References	Validated Measure	Study Population	N	Administrative Health Data Source	Reference Standard	Study Findings				Limitations
							Sensitivity-% (CI)	Specificity-% (CI)	PPV-% (CI)	NPV-% (CI)	
Garland et al. (55)	AKI-RRT	Adults (aged 40 years or older), requiring life support, admitted to 11 adult ICUs in Canada between 2007 and 2012	20,764 hospitalizations involving 17,624 unique individuals	Intra-hospital administrative database using ICD-10 diagnostic and procedure codes. For RRT, codes representing intermittent or continuous HD, excluding PD, were used	Clinical data from combined Winnipeg ICU database and Manitoba dialysis registry	HD Codes	92.2 (90.2–93.8)	96.6 (96.3–96.9)	55.4 (52.8–57.9)	99.6 (99.5–99.7)	- Single-center data may limit generalizability - Absence of a "gold standard," Reference standard did not use chart reviewed data and confirm AKI using SCr or UO data
						Above + HD Catheter Codes	92.3 (90.3–93.9)	96.2 (96.0–96.5)	52.8 (50.3–55.3)	99.6 (99.5–99.7)	
						Above + ARF Diagnostic Codes	94.5 (92.8–95.9)	86.7 (86.2–87.1)	24.4 (23.0–25.9)	99.7 (99.6–99.8)	

ACS' NSQIP, American College of Surgeons' National Surgical Quality Improvement Program; AKI, acute kidney injury; AKI-RRT, AKI receiving renal replacement therapy; AMI, acute myocardial infarction; ARF, acute renal failure; CABG, coronary artery bypass graft; CI, confidence interval; CRRT, continuous renal replacement therapy; ESRD, end-stage renal disease; HD, hemodialysis; ICD-9, International Classification of Disease, Ninth Revision; ICD-10, International Classification of Disease, Tenth Revision; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; NHDS, National Hospital Discharge Survey; NIS, Nationwide Inpatient Sample; NPV, negative predictive value; NR, not reported; PD, peritoneal dialysis; PPV, positive predictive value; SCr, serum creatinine; UO, urine output.

did not improve sensitivity of administrative health care data, relative to chart review, using creatinine only (sensitivity 11.7 vs. 17.4%) (51). Of note, the authors used KDIGO criteria for creatinine, but a more stringent definition for urine output, to improve sensitivity. In another study of children admitted to ICU, sensitivity was also not improved when using creatinine or urine output criteria, relative to creatinine alone (53). However, urine output criteria alone, relative to creatinine alone, had higher sensitivity for detecting any AKI (13.7 vs. 5.9%) and for detecting stage 2 or worse AKI (18.2 vs. 14.1%). NPV was more variable (49.4–99.7%), but most reported an NPV of >80%. PPV was more variable (24.4–100%), but most reported PPV of >50%. These results are consistent with those published in an earlier systematic review (47).

There are a number of limitations when validating administrative data for AKI. The most significant problems are related to the fact that the definition of AKI has changed significantly in the past 15 years, which is certainly a source of misclassification bias of AKI outcomes (16). Although oliguria has been associated with increased mortality in ICU populations and is an important component of the KDIGO definition (3, 63), urine output data are also difficult to extract from administrative databases and even chart review (51). Most validation studies have used creatinine criteria alone. Further validation studies are required to validate the use of billing codes using KDIGO criteria, different stages of severity, and inclusion of serum creatinine and/or urine output criteria for use in administrative health research.

There are additional challenges with validity when interpreting data based on physician billing codes. Physician billing practices change as our understanding of the significant morbidity and mortality associated with AKI evolves over time. For example, it is unclear whether practice changes are responsible for the increasing incidence of AKI observed from administrative health studies; however, the only study comparing administrative data at different time periods (2005 vs. 2010) did not show any significant change in PPV over time (50). Many administrative databases report only a limited number of billing codes; therefore, patients with milder AKI may be underrepresented. As well, billing codes have continued and will continue to change over time, requiring repeated validation of newer codes (16, 64). However, one study comparing administrative data derived from *ICD-9* vs. *ICD-10* billing codes showed no change in sensitivity (80.0%) and only a small decrease in specificity (98.3 vs. 95.5%), respectively (59).

Another major issue is limited generalizability, or external validity, given the significant heterogeneity of these studies (16). For example, the study by D'Arienzo et al. suggests that sensitivity may be lower in pediatric patients with milder AKI and/or post–cardiac surgery (53). The study by Schaffzin et al. suggests that sensitivity is lower in pediatric patients with nephrotoxin-related AKI (49). These results reflect the significant heterogeneity in the populations studied, including age, disease severity, and etiology of AKI. Furthermore, practice standards are highly variable for the recognition and management of AKI, and this may be different across countries or academic vs. community centers. The reference standard is usually based on standardized

chart review at one to two academic centers; these results may not be generalizable to nationwide practice for patients with AKI. Finally, administrative databases may not capture certain segments of the population in countries where there is both universal public and private health care systems and/or large uninsured populations (16).

In summary, these validation studies continue to be limited by variable definitions for AKI, significant heterogeneity of data sources and population studies, and reduced generalizability. Future studies are needed to further validate subpopulations, particularly in the pediatric population; as well, standardized guidelines for defining AKI using discharge billing codes will be essential in improving the applicability of administrative data to AKI health research (19).

EPIDEMIOLOGY AND OUTCOMES OF AKI

Administrative health research has served as an important methodological source for a number of observational epidemiology studies, which have fundamentally changed our understanding of AKI. This section will focus on studies in AKI conducted using administrative health data in the past 5 years.

Incidence

AKI is common in hospitalized patients with particularly high incidence rates seen in critically ill, post–cardiac surgery, oncology, and nephrotoxin-exposed adults and children (1, 3, 62, 65, 66). However, there have been conflicting results regarding the changing temporal trends in AKI and AKI receiving KRT. One of the first studies used a national database to identify cases of AKI receiving KRT using *ICD-9* codes and found that from 2000 to 2009, the incidence had increased by an average of 10% per year (67). Another study identified more than 18,000 adult patients with AKI receiving KRT using *ICD-10* codes between 2000 and 2012 (68). The authors found that the crude incidence rate of AKI receiving KRT increased nearly 3-fold from 2000 to 2006; although the rate of growth remained stable between 2006 and 2012, the use of continuous renal replacement therapy (CRRT) increased throughout this period and especially in patients >75 years with high comorbid disease. In children, a similar trend of dialysis receiving AKI has been reported (69). Our group found an increasing trend in the incidence of AKI, as well as use of hemodialysis and CRRT among hospitalized children (1 month to 18 years) in Ontario, Canada (69). However, another large study, which compared the annual AKI incidence rate using data from an electronic health record surveillance tool and administrative data (70), found no difference in AKI incidence between 2006 and 2014 when adjusted for age and sex using either data source.

Short-Term Outcomes

Health administrative databases have improved our understanding that AKI is independently associated with increased hospital mortality and morbidity, including length of hospital and ICU stay, and increased health care costs. One study in Japan across more than 280 hospitals showed a decreasing trend in crude in-hospital mortality from 45% in 2007 to 36% in 2016 (71). An Italian study showed in-hospital mortality rate of nearly 30% with the highest risk being in patients with AKI receiving KRT [odds ratio, 2.7; 95% confidence interval (CI), 2.7–2.8] (72). Finally, another Canadian study showed mortality rates between 30 and 40% for adult patients with AKI receiving KRT, but no association with increased mortality in centers who manage a lower volume of patients requiring KRT (73). The Canadian study in children with AKI receiving KRT also examined 30-day mortality, finding an increased rate from 14 to 25% between 1996 and 2009, although this rate subsequently decreased to 19% by 2015 (69). Another study in Japan included pediatric patients (>12 years) and reported 50% in-hospital mortality rate for patients treated with CRRT (74).

Several studies have also described rates of renal recovery, as well as the recurrence risk after AKI, both of which reflect a growing appreciation for AKI as a dynamic process (75–78). A study of critically ill children in Canada showed that children with stage 3 AKI were more than 3-fold likely to have elevated serum creatinine at discharge (>1.5× baseline), relative to those without stage 3 AKI (79). A small study examined children who received ventricular assist devices (VADs) for heart failure and subsequently went on to undergo heart transplant (80). Those children without renal recovery (serum creatinine ≥1.5× baseline) 7 days after VAD implantation, relative to children who had full recovery, were not at increased risk for CKD at 1 year following heart transplant; however, those with reduced estimated glomerular filtration rate 1 month after VAD implantation were at increased risk for CKD.

There is also increased interest in the relative cost and burden associated with AKI. One study in Alberta, Canada, estimated the incremental cost of AKI to be more than Canadian $200 million per year (81). Patients with AKI receiving KRT had prolonged length of stay by more than 7 days and increased cost by up to $20,000, relative to patients without AKI. Another large study of adults from Alberta, Canada, undergoing cardiac surgery also showed increased length of stay and costs associated with increased AKI severity (82).

Risk Factors

Risk factors for AKI in hospitalized patients include extremes of age, underlying illness (i.e., sepsis, cardiovascular disease with or without bypass surgery, oncologic disease), nephrotoxin exposure, inflammatory mediators (i.e., cytokine release), and disease severity (62, 75, 83–89). A large study in the United States of 3.6 million postsurgical patients found that AKI was common postoperatively, affecting more than 10% of hospitalized patients (86). AKI in patients with CKD is also an important risk factor for subsequent progression to ESKD (88). One study highlighted that patients who progressed from stage 3 to stage 4 CKD also had a high risk for AKI (89). Other subpopulations noted to be at increased risk for AKI-related morbidity and mortality include adults with decompensated liver disease (90) and stroke (91).

A number of studies have examined the impact of nephrotoxic medications using administrative health data (92–98). One study in hospitalized children across six of the largest children's hospitals in the United States found that combined use of vancomycin with piperacillin/tazobactam conferred more than 3-fold increased risk for antibiotic-associated AKI, relative

to vancomycin with another antipseudomonal antibiotic (93). Other nephrotoxins examined include non-steroidal anti-inflammatory drugs in young, healthy adults (94), brands and dosing of immunoglobulin products (95), and statin use in elderly patients (96), all of which showed modest associations with AKI. Administrative data were also used to develop an evidence-based nephrotoxin medication list that could be used as part of a screening program for AKI in children (98).

Long-Term Outcomes

AKI is associated with increased risk for development of cardiovascular disease, CKD, and ESKD in adults (1, 75, 78, 83, 99). A study in Northern California, including more than 43,000 patients, showed that AKI in adults is independently associated with HTN as early as 6 months after initial event (99). Another large study of more than 100,000 patients in the United States showed that more than 30% of hospitalized adults with AKI went on to develop CKD at 1-year follow-up (78).

The risks of long-term kidney and cardiovascular sequelae after pediatric AKI remain uncertain, at least partially due to the fact that studies have lacked comparator cohorts, have had high losses to follow-up, and/or have had short follow-up periods. Recent prospective cohort studies have conflicting results; TRIBE-AKI, FRAIL-AKI, and ASSESS-AKI all found that cardiac surgery–associated AKI survivors have similar 4–7-year kidney outcomes vs. children without AKI (24–26), whereas Benisty et al. found higher long-term risks of CKD and HTN among survivors of ICU-associated AKI (27). Although there is a clear signal of increased CKD risk among pediatric AKI survivors in other cohort studies (6, 13, 28–30), the long-term outcomes after episodes of dialysis-receiving AKI remain uncertain.

Health administrative databases provide a unique opportunity to follow children many years after an episode of AKI, even after the age of 18 years, to study their long-term outcomes. Moreover, CKD and HTN-related cardiovascular changes start early in life; therefore, it is essential to understand the timing and magnitude of the onset of these events after an episode of AKI, so that appropriate treatment can be initiated in time to address these risk factors and avoid or delay future cardiovascular disease (100). Current AKI guidelines in neonates and children do not provide recommendations for long-term follow-up, primarily due to a lack of studies with robust data.

Several studies have examined long-term outcomes in hospitalized children with AKI. A recent study from Ontario using administrative health data with median 10-year follow-up compared children surviving AKI receiving KRT with hospital-matched controls (101). The authors found that these children had significantly increased hazard for major adverse kidney events (composite outcome of kidney failure and all-cause mortality) [adjusted hazard ratio (HR), 4.97; 95% CI, 4.04–6.10], CKD (adjusted HR, 8.70; 95% CI, 6.68–11.34), and HTN (adjusted HR, 3.35; 95% CI, 2.59–4.33). Another cohort of critically ill children with AKI in Quebec was also found to have increased risk for mortality 5–7 years following hospital discharge, relative to children without AKI (adjusted HR, 3.1; 95% CI, 1.5–6.6) (6). Health care utilization was also increased for critically ill children with AKI, relative to children without AKI, including increased hospitalizations and physician visits at 5 years following hospital discharge (7). This cohort also had increased risk for HTN (adjusted HR, 2.19; 95% CI, 1.47–3.26) (9) and CKD (adjusted HR, 2.2; 95% CI, 1.1–4.5) (8) at 5-year follow-up, defined using administrative health care data. Another study following critically ill children with congenital heart disease showed that those who developed AKI within 5 days of cardiac surgery were at significantly increased risk for CKD at 5 years, relative to those who did not develop AKI (HR, 3.8; 95% CI, 1.4–10.4) (102). We have also previously reported that, among children who underwent cardiac surgery for congenital heart disease, those who received dialysis for AKI during their index cardiac surgery admission were at a 5-fold higher risk of ESKD (crude HR, 5.0; 95% CI, 2.0–12.6) compared with those who did not receive dialysis during their cardiac surgery admission (103).

CONCLUSION

Our understanding of AKI has undergone a significant transformation over the past 15 years partly due to methodological advances in which AKI has been studied by epidemiologists (1). Hand-in-hand with a veritable explosion of research demonstrating the morbidity and mortality related to AKI in adults and children, there has been significant attention paid to "big data" (18, 25, 37). Registries containing administrative health care data are readily available, efficient, and large (14, 19). Validation studies have been shown that administrative health care data are highly specific, despite having modest sensitivity, for the diagnosis of AKI. There are important limitations as well, including heterogeneity of data sources and inconsistent reporting on specific outcome measures (i.e., quality of life, patient-reported outcomes). The statements from the ADQI consensus conference recognized many strategies by which administrative health data could be applied to AKI-specific research studies and address knowledge gaps in the field (18–23).

Studies using administrative health care data have expanded our understanding of the incidence, risk factors, and outcomes of AKI in both adults and children. Importantly, we have demonstrated that these clinically relevant findings have been supported by results from traditional data sources. Continued progress in the application of large data sources to epidemiological studies will continue to further our understanding of important patient-related outcomes of adults and children with AKI.

AUTHOR CONTRIBUTIONS

EU drafted the manuscript, prepared the figures, and reviewed and revised the manuscript. GS also contributed to the manuscript and reviewed and revised the manuscript. RC supervised the manuscript preparation and reviewed and revised the manuscript for intellectual content. MZ reviewed and revised the manuscript for intellectual content. All authors approved the final manuscript as submitted.

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