Acute Kidney Injury in Critically Ill Children: Epidemiology, Risk Factors, and Outcomes

by

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ABSTRACT

Background:

Acute kidney injury (AKI) is common in critically ill children. The development of AKI is not a trivial complication. Accumulating data show suboptimal short-term and poor long-term outcomes after an episode of AKI. Understanding the epidemiology of AKI in the pediatric population and identification of those at greatest risk is critical. The current evidence base is limited by number of factors: 1) The population-based incidence of AKI in critically ill children has not been examined. The majority of AKI studies in pediatric populations have been single center with relatively small numbers necessitating validation using larger cohorts. 2) Existing pediatric studies have used diverse AKI definitions. There are limited pediatric studies that have applied the KDIGO consensus criteria to describe the epidemiology and outcome of AKI in PICU. 3) Existing evidence suggest fluid overload plays an important role in the pathophysiology of AKI and have significant potential to modify outcomes. However, this relationship has not been thoroughly evaluated in the pediatric population. 4) Finally, the methods to assess fluid balance and define fluid overload are inconsistently described in the literature.

Methods:

In order to address these knowledge gaps, two methods were used in this thesis. First, I conducted a population-based multicentre cohort study to evaluate the epidemiology of AKI, associated risk factors and outcomes. All children admitted to three pediatric intensive care units (PICU) in Alberta, Canada between January 1 to December 31, 2015, utilizing prospectively collected data from a bedside clinical information system and data repository, were included.

Second, I performed a systematic review and meta-analysis to describe the methods used to measure fluid balance, define fluid overload, and evaluate the association between fluid balance and outcomes in critically ill children.

Results:

In the first part of the thesis, a total of 1017 patients were included. AKI developed in 308 patients (30.3%; 95% CI, 28.1% to 33.8%) and severe AKI (KDIGO stage 2 and 3) developed in 124 patients (12.2%; 95% CI, 10.3% to 14.4%). Incidence rates for critical illness-associated AKI and severe AKI were 34 (95% CI, 30.3 to 38.0) and 14 (95% CI, 11.38 to 16.38) per 100,000 children-year, respectively. Thirty-two patients (3.1%) did not survive to PICU discharge. The AKI-associated PICU mortality rate was 2.3 (95% CI, 1.4 to 3.5) per 100,000 children-year. After adjustment for weight, case-mix, illness acuity (Pediatric Index of Mortality 3) and PICU site, severe AKI was associated with greater PICU mortality (odds ratio [OR] 11.93; 95% CI, 4.68 to 30.42) and 1-year mortality (OR 5.50, 95% CI, 2.76 to 10.96). Severe AKI was further associated with greater duration of mechanical ventilation, duration of vasoactive support and lengths of PICU and hospital stay.

In the second part, the systematic review and meta-analysis, a total of 44 studies (7507 children) were included. Fluid overload, however defined, was associated with increased in-hospital mortality (17 studies [n = 2853]; odds ratio [OR], 4.34 [95% CI, 3.01-6.26]; I2 = 61%). Survivors had lower percentage fluid overload than non-survivors (22 studies [n = 2848]; mean difference, −5.62 [95% CI, −7.28 to −3.97]; I2 = 76%). After adjustment for illness severity,

there was a 6% increase in odds of mortality for every 1% increase in percentage fluid overload (11 studies [n = 3200]; adjusted OR, 1.06 [95% CI, 1.03-1.10]; I2 = 66%). Fluid overload was associated with increased risk for prolonged mechanical ventilation (>48 hours) (3 studies [n = 631]; OR, 2.14 [95% CI, 1.25-3.66]; I2 = 0%) and acute kidney injury (7 studies [n = 1833]; OR, 2.36 [95% CI, 1.27-4.38]; I2 = 78%).

Conclusion

The population-level burden of AKI and its attributable risks, including greater mortality and health services use, are considerable among critically ill children. These findings emphasize the need for enhanced surveillance for AKI, identification of modifiable risks and evaluation of interventional strategies. Fluid overload could represent a modifiable risk factor and a target for intervention in critically ill children, particularly for those with or at risk of AKI. The findings suggest fluid overload is associated with substantial morbidity and mortality in this population. Additional research should now ideally focus on interventions aimed to mitigate the potential for harm associated with fluid overload.

PREFACE

This thesis is an original work by Rashid Alobaidi.

An adopted version of Chapter 1 has been published as a book chapter titled "Acute Kidney Injury" in Surgical Intensive Care Medicine. O'Donell J, Nacul M. 3rd Edition. New York: Springer Publishing (2016), with Dr. Sean Bagshaw as co-author.

Chapter 2 received approval by the University of Alberta Health Research Ethics Board (REB File # PRO00063318). The need for written informed consent was waived.

Chapter 3 has been published as *Alobaidi R, Morgan C, Basu RK, Stenson E, Featherstone R, Majumdar SR, et al. Association Between Fluid Balance and Outcomes in Critically Ill Children: A protocol for Systematic Review and Meta-analysis. Can J Kidney Health Dis. 2017; 4*. I was responsible for study concept and drafting of the manuscript.

Chapter 4 has been published as *Alobaidi R, Morgan C, Basu RK, Stenson E, Featherstone R, Majumdar SR, et al. Association Between Fluid Balance and Outcomes in Critically Ill Children: A Systematic Review and Meta-analysis. JAMA Pediatr. 2018;172(3):257-68*. I was responsible for study concept, screening of studies, data extraction, statistical analysis, and drafting of the manuscript. Dr. Stenson helped with screening of studies and data extraction. Ms. Featherstone developed and conducted the literature search.

Dedicated

to the loves of my life

Azhar, Norah and Alya

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CHAPTER 1

Introduction to Acute Kidney Injury in Critically Ill Patients

Acute kidney injury (AKI), now replacing the term acute renal failure, is a broad clinical syndrome characterized by rapid deterioration of kidney function that results in failure to maintain fluid, electrolyte, and acid–base homoeostasis, concomitant with the retention of nitrogenous waste products. The new term implies that AKI represents a spectrum encompassing kidney insults that may possibly exist long before overt kidney failure occurs. AKI is exceedingly common, particularly in the critically ill patients. The magnitude of AKI and its strong association with poor outcome, coupled with the paucity of specific treatment options, make it a challenging clinical problem. In that regard, preventative strategies and early identification are of high importance to improve outcomes for those at risk of or with early evidence of AKI.

1.1 AKI Definition

There have been long-standing challenges for arriving at a unified definition of AKI. In response, a more standardized consensus definition, known as the RIFLE criteria, was proposed. This classification scheme provides an operational definition for AKI and stratifies it into categories of severity (Risk; Injury; Failure and End-stage kidney disease) (1). Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI group proposed further refinement and harmonization to this classification scheme (2). The KDIGO classification defines AKI as the rapid deterioration of kidney function that is associated with any of the following: (a) increase in serum creatinine by ≥0.3 mg/dL (26.5 μmol/L) within 48 h; (b) an increase in serum creatinine ≥1.5 times above baseline over 7 days; and/or (c) oliguria with urine output <0.5

mL/kg/h over 6 h (Table 1.1). The KDIGO classification utilizes absolute and relative changes in serum creatinine level and urine output to define and assess the severity of kidney injury.

1.2 AKI Diagnosis

1.2.1 Serum Creatinine and urine output

While the KDIGO classification is an important advance in the field of AKI, use of creatinine and urine output have limitations. The most important is that serum creatinine is not an indicator of "injury" per se but rather a surrogate marker of function, with its own limitations. First, serum creatinine values can vary widely by age, sex, diet, muscle mass, and the volume status of the patient. Numerous drugs (e.g., trimethoprim, cimetidine) and acute physiologic states (e.g., sepsis, rhabdomyolysis, fluid overload) can influence serum creatinine levels (3). Second, changes to serum creatinine can be delayed, often requiring >24 h to reach a new steady state after acute changes to glomerular filtration rate (GFR). Moreover, due to the nonlinear relationship between GFR and serum creatinine, GFR may decrease by more than 50 % prior to significant increments in serum creatinine occurring (4). Some data suggest that the use of urine output of 0.5 mL/kg/h might be too sensitive in detecting AKI (5). While an episode of oliguria may not always be followed by increments in serum creatinine consistent with AKI, oliguria still remains a valuable bedside predictor of early changes on kidney function (6, 7). Recent evidence has shown a strong association between the duration and frequency of episodes of oliguria and higher mortality (8, 9).

1.2.2 Urine Biochemistry

The role of classic urine biochemistry and derived indices in the diagnosis and discrimination of AKI remains controversial (10). Data from observational studies have found

many of these parameters, in particular urine sodium (UNa), and the fractional excretion of sodium and urea (FeNa, FeU) have relatively poor operative characteristics for the majority of hospitalized patients to inform about diagnosis and provide clinical decision support (11). On the other hand, recent work has shown an evaluation of the urinary sediment for renal epithelial cells and casts can provide prognostic information about the risk for worsening AKI (12). A prospective evaluation of a urine microscopy score derived from renal tubular cells and casts correlated with urinary neutrophil gelatinase-associated lipocalin (NGAL) levels and with severity of AKI (13).

1.2.3 Novel Kidney Damage Biomarkers

The precise role of novel kidney damage biomarkers such as cystatin C, neutrophil gelatinase-associated lipocalin [NGAL], insulin-like growth factor-binding protein 7 [IGFBP7], and tissue inhibitor of metalloproteinases-2 [TIMP-2]; kidney injury molecule-1; interleukin-18; L-type fatty acid-binding protein detectable in the blood and urine for the diagnosis of AKI and for clinical decision support, while very promising, are still undergoing investigation. For instance, novel biomarkers have shown an ability to identify AKI in septic patients before changes in serum creatinine levels. Plasma and urine NGAL levels were significantly higher at 0, 12, and 24 hours in 83 patients with sepsis-associated AKI compared with patients with non-septic AKI (14). While other studies showed inconsistent findings, a systematic review that included 15 studies evaluating plasma and urine NGAL in septic patients suggested that they have good precision in diagnosing AKI and predicting outcome including receipt of RRT and mortality (15).

1.2.4 Risk Prediction Tools

Risk prediction tools can be utilized to identify patients at greater risk of developing overt or worsening AKI. For example, the concept of renal angina index (RAI), a composite based on risk factors and early signs of kidney injury, has shown good predictive performance in severe AKI in critically ill children (Table 1.2) (16). Modern clinical information systems can be designed to trigger alerts to clinicians for "at-risk" patients who are developing early AKI or who are exposed to unnecessary nephrotoxins. The use of automated alerting from clinical information systems that can integrate bedside information (i.e., urine output), laboratory information (i.e., absolute and relative changes in serum creatinine), and pharmacy information (i.e., potential nephrotoxin exposure) have been shown to improve the recognition of AKI in hospitalized patients (17, 18).

1.3 AKI Epidemiology

The lack of universally accepted AKI definition in the past has made accurate assessment of AKI epidemiology challenging. Nevertheless, recent data have shown rising trends in the incidence of hospital-acquired AKI. While this is partly attributable to improved recognition and more consistent reporting with the integration of consensus definitions, changes to the population baseline susceptibilities (e.g. comorbid conditions such as congenital heart disease) and greater iatrogenic exposures to AKI risk factors in the community and during acute hospitalizations (i.e., drugs, diagnostic investigations, complex procedures) have also contributed. In a recent systematic review of worldwide incidence of AKI, a large cohort of 312 studies that included over 49 million patients found that AKI (using the KDIGO definition) affects one in five adults and one in three children during hospital admission (19). A large Australian retrospective cohort

(n = 20,126) reported 18 % incidence of AKI in hospitalized patients using the RIFLE criteria (20). In ICU settings, the incidence rate of AKI was estimated at 180 per 100,000 person-years (21) with the incidence of AKI reported to be at 58% (22). Several hospital-based pediatric studies, applying different AKI definitions, have described the incidence of AKI to be between 16-58% (Table 1.3) (23-32). More recently, the Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults (AWARE) study evaluated the incidence of AKI in a large prospective multinational cohort of critically ill children. AKI occurred in 27% and severe AKI occurred in 12% of the patients (33).

1.4 AKI Associated Outcomes

The development of AKI has negative effects on both short- and long-term outcomes. The severity of AKI also correlates with increased mortality, with patients treated with RRT having highest mortality rates, reaching as high as 60 % (20, 22, 34). In AWARE, critically ill children with severe AKI had higher mortality (adjusted odds ratio, 1.77; 95% CI, 1.17 to 2.68) (33).

AKI is also associated with significant morbidity. AKI leads to greater susceptibility to infection/sepsis, prolonged duration and delayed weaning from mechanical ventilation, and longer or unanticipated stays in ICU and hospital (35). Perhaps more importantly, AKI is a clear risk factor for development of CKD. Survivors of AKI have higher rates of incident CKD and accelerated progression to end-stage kidney disease (ESKD) and dialysis dependence. In those with severe AKI requiring RRT, the rates of non-recovery and dialysis dependence at hospital discharge range between 13 and 29 % (36, 37). Limited pediatric data described the long-term

recovery and occurrence of chronic kidney disease (CKD) among surviving children with AKI. A prospective pediatric cohort study reported that CKD, defined as GFR <60 mL/min/1.73 m^2, developed in approximately 10% of AKI occurring in PICU patients within 1-3 years (38). In addition to CKD, recent data have also suggested that survivors of AKI remain at increased long-term risk infection, major cardiovascular events, malignancy, and higher health services use. Several studies have now reported the health-related quality of life after AKI is significantly impaired when compared to population norms. Consequently, AKI has significant implications on health care resource use and costs (35). A US study reported that an episode of AKI (defined as KDIGO stage 2) during hospitalization was associated with an excess US$9000 in hospital costs (39).

1.5 AKI Clinical Presentation

The clinical presentation of AKI may vary according to the etiology and the severity. AKI may be clinically silent until there are overt changes to serum creatinine (which is dependent on serum creatinine being routinely monitored in "at-risk" patients) and/or urine output. Urine output is often, but not always, decreased. As kidney function worsens, electrolyte disturbances (i.e., hyperkalemia, hyperphosphatemia), metabolic acidosis due to diminished clearance of acid, and fluid accumulation occur. If patients with AKI are not carefully monitored or untreated, disruption of metabolic and fluid balance homeostasis can lead to life-threatening complications such as ventricular arrhythmias and pulmonary edema.

The contributing factors for AKI can largely be categorized into conditions that alter renal hemodynamics, conditions that cause direct kidney injury, or conditions that contribute to the

obstruction of urine flow. Often critically ill patients will present with multiple concurrent and temporally associated contributing factors for AKI. The early identification of precipitating causes is essential for limiting the extent of ongoing injury and promoting repair and recovery. Alternation to kidney hemodynamics, due to either or both systemic and regional factors, is likely the most common etiology for AKI in the ICU. These include events that affect systemic hemodynamics by causing a decrease in extracellular volume (e.g., hypovolemia, dehydration, hemorrhage, burns), redistribution of that volume (e.g., postoperative "third" space loss, capillary leak in sepsis, pancreatitis, or hepatic failure), or events associated with decreased cardiac output (e.g., heart failure and septic shock). Kidney function can also be impacted by alterations to regional kidney hemodynamics. Processes that alter afferent (e.g., non-steroidal anti-inflammatory drugs) and/or efferent arteriolar tone (e.g., angiotensin converting enzyme inhibitors and Angiotensin II receptor blockers) can adversely impact glomerular filtration. Complete anuria is uncommon; however, it can be the harbinger of severe kidney injury. It can result from bilateral damage to the ureters (e.g., retroperitoneal malignancy or hemorrhage), obstruction of the bladder or urethra from stones, clots, or malposition or malfunctioning indwelling catheters. The use of medications that lead to urinary retention in those without an indwelling urinary catheter may exacerbate the presentation.

1.5.1 Sepsis-associated AKI

Sepsis is the most common contributing factor for AKI among hospitalized and critically ill patients. An estimated 50 % of patients with sepsis develop AKI (40). Moreover, the development of AKI among hospitalized patients is associated with greater risk for development of sepsis due to alterations in immune function. The pathophysiology of AKI in sepsis is

complex and includes systemic and inter-renal hemodynamic mechanisms, renal microcirculatory dysfunction, and activation of immune and inflammatory pathways resulting in direct renal injury (40).

1.5.2 Nephrotoxin Exposure

There are numerous exogenous (mostly drugs) and endogenous toxins (e.g., inflammatory mediators, hemoglobin, myoglobin, uric acid) that contribute to AKI in susceptible patients. Importantly, patients are often exposed to multiple nephrotoxins during their course in hospital. Among those with AKI, nephrotoxin exposures often occur without sufficient opportunity for renal recovery. These repeated insults are recognized as important contributors to extension of acute injury, maladaptive renal repair, and greater risk for the development of CKD. Their toxic effects may be precipitated by a number of mechanisms including altered renal autoregulation and hemodynamics, direct tubular toxicity, interstitial nephritis, and intra-tubular obstruction due to crystal precipitation (18). A list of selected nephrotoxic drugs commonly prescribed in hospitalized patients is shown in Table 1.4.

1.5.3 Intra-abdominal hypertension/abdominal compartment Syndrome

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) can worsen kidney function and precipitate AKI. Mechanical compression on abdominal and thoracic vessels results in diminished venous return, congestion, increased renal venous pressure, which leads to renal interstitial edema. This coupled with renal arterial vasoconstriction due to compensatory renin–angiotensin–aldosterone system activation contributes to impaired perfusion pressure across the renal circulation. Patients with IAH progressing to ACS commonly present

with abdominal distension, measured intra-abdominal pressure > 15 mmHg, and increasing serum creatinine and oliguria. ACS is commonly associated with major trauma or large burn injuries, complex intra-abdominal surgeries, pancreatitis, and in patients receiving large volume resuscitation (41).

1.5.4 Rhabdomyolysis

Rhabdomyolysis is a common precipitant for myoglobinuric AKI. Rhabdomyolysis may be precipitated by a variety of conditions including those that result in direct muscle damage (e.g., crush injury, burns, major trauma, electrical injury, myositis), decreased muscle supply of oxygen and/or substrates (e.g., surgical clamping, compartment syndrome, emboli), excessive metabolic demand (e.g., strenuous exercise, seizures, substance abuse), impaired cellular energy production (e.g., hereditary enzyme disorders, toxins), and increased calcium influx (e.g., malignant hyperthermia). Myoglobin released from injured muscles precipitates in the renal tubules and contributes to tubular obstruction. It also has a direct toxic effect on the kidneys. Intravascular volume depletion due to fluid sequestration in injured muscles contributes to relative hypovolemia and renal hypoperfusion. The presence of high serum creatine kinase and myoglobinuria with pigmented casts and dark-colored urine confirm the diagnosis.

1.5.5 Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a form of AKI occurring in patients with advanced hepatic dysfunction and portal hypertension. It occurs in 40 % of patients with advanced cirrhosis within 5 years. It presents with worsening renal function and oliguria associated with significant fluid retention and hyponatremia. The pathophysiology of HRS is complex but

includes mechanisms that contribute to relative hypovolemia, systemic, and splanchnic vasodilatation; activation of the renin–angiotensin–aldosterone activation with avid sodium retention; followed by progressive renal vasoconstriction (42).

1.6 AKI Management

The general principles in the evaluation and management of AKI are aimed at limiting injury, avoiding life-threatening complications, and facilitating recovery. This is followed by therapy that is tailored to the specific clinical picture and underlying etiology, with an overall emphasis on eliminating any potential contributors to worsening kidney function and treating disturbances of physiological homeostasis.

1.6.1 Resuscitation and Optimization of Volume Status

Regardless of the cause of AKI, ensuring optimal blood flow and perfusion pressure to the kidneys should always be a priority. This helps prevent the progression of the insult and development of secondary intrinsic renal injury. When shock is identified, resuscitation and optimization of intravascular volume should be performed promptly by the administration of fluid and vasoactive therapy titrated to physiological endpoints (i.e., mean arterial pressure, heart rate, central venous oxygen saturation, serum lactate, urine output) (2).

Recent data have provided insight into the type of fluid that should be used for resuscitation in patients with or at elevated risk for AKI. The composition of crystalloid solutions and the risk of adverse kidney sequelae have been examined. The preferential use of balanced crystalloid solutions (such as Ringer's lactate and Plasmalyte) has been shown to reduce the risk

of iatrogenic metabolic acidosis, AKI and mortality. A recent large randomized cross-over trial showed the use of balanced crystalloids to be associated with lower occurrence of composite outcome (mortality, RRT and persistent renal dysfunction) (43). The issue of the ideal crystalloid solution for acute resuscitation to optimize kidney and patient survival remains to be definitively proven. The use of albumin in acute resuscitation remains controversial. A secondary analysis of the SAFE study and a systematic review have shown use of albumin solutions are associated with reduced mortality; however, no significant difference in the incidence of AKI (44, 45). Although the ALBIOS trial showed that albumin replacement in sepsis was not associated with survival benefit, a post-hoc analysis suggested albumin-containing solutions may improve the hemodynamic profile, reduce fluid volumes and organ dysfunction in patients with septic shock (46). However, there remains a number of uncertainties regarding the routine use of albumin for resuscitation of critically ill patients. Recent randomized controlled trials have shown that the use of colloid solutions containing HES for resuscitation in critically ill patients and those with severe sepsis and septic shock contribute to increased risk of AKI, severe AKI requiring treatment with RRT, and death. HES solutions, including newer lower molecular weight/molar substitution solutions (i.e., 140/0.32), should be avoided (47, 48).

Patients no longer "fluid responsive" should be carefully monitored for complications of fluid accumulation and overload, such as pulmonary edema, ileus, and intra-abdominal hypertension. Unnecessary fluid loading in general, but in particular in patients with impaired excretory function due to AKI, can be a risk for iatrogenic harm. Fluid overload in AKI is associated with less favorable outcomes including higher utilization of RRT, higher mortality, and reduced probability of renal recovery (49, 50). Fluid balance should be meticulously

measured in all critically ill patients by documenting the measured differences between intake/ output and weights. In patients developing complications attributable to fluid accumulation, efforts should be made to minimize all nonessential fluid administration along with, if applicable, active fluid removal with diuretic therapy or initiation of RRT.

1.6.2 Vasoactive Support

Specific to AKI, the use of "renal-dose" dopamine has not proven effective for preventing the development of AKI (51). Some data from adult populations suggest potential renal benefits from using vasopressin in septic shock including minimize the progression of AKI and less utilization of RRT (52, 53). However, these findings were not associated with significant decrease in mortality. The use of vasopressin in pediatric vasodilatory shock was evaluated in a multicenter RCT (54). The study showed a non-significant trend of increased mortality in those receiving vasopressin. There was no difference in creatinine level between the two groups. Based on the lack of observed clinical benefits and potential of harm, the routine use of vasopressin in pediatric septic shock is currently not recommended. Fenoldopam (selective Dopamine receptor-1 agonist) was found to have protective effect against the development of SA-AKI in a small RCT; however, did shown a survival benefit, suggesting the need for further verification in high-quality trials (55). Use of recombinant angiotensin II (ANGII) infusion as a novel vasopressor has shown kidney-specific benefits in experimental sepsis models. A recent phase 3 RCT evaluating the use of ANGII showed significant improvements in mean arterial pressure in patients with catecholamine-resistant vasodilatory shock compared to placebo (56). Further trials are anticipated to evaluate whether these findings can further translate to survival and kidney benefits.

1.6.3 Avoidance of Nephrotoxins

In patients with established AKI, as well in those at increased risk, avoidance of nephrotoxin is a priority to prevent overt or worsening AKI and delay of renal recovery. In circumstances where there are no options other than to use a nephrotoxin, therapeutic drug monitoring and careful dose adjustment in multidisciplinary consultation with pharmacy should be undertaken. The perceived benefits and risk of receiving contrast media for diagnostic imaging should be carefully evaluated; and where applicable, delay or choosing alternative imaging modalities should be undertaking in those at high risk where possible.

1.6.4 Diuretic Therapy

The routine use of diuretic agents in AKI remains controversial. Whether diuretics, in particular loop diuretics, have a reno-protective role by inhibiting the NaK2Cl transporter in the thick ascending loop of Henle and reducing medullary oxygen demand is unclear. However, loop diuretics have an important role in maintaining fluid balance homeostasis in hospitalized patients with a high obligatory daily fluid intake at risk for complications related to fluid accumulation. Loop diuretics have been suggested to reduce the risk of AKI by theoretically "flushing" the renal tubules of debris, augmenting intra-renal medullary blood flow, reducing kidney oxygen consumption, and reducing maladaptive gene upregulation and renal tissue apoptosis. Available evidence, however, has been inconsistent in showing improvement in clinical outcomes associated with loop diuretic use in AKI (57, 58).

1.6.6 Renal Replacement Therapy

Despite supportive therapy, kidney function might be lost in some patients and RRT might be indicated. The decision to start RRT is often complex and shows considerable variability. RRT should be initiated when confronted with life-threatening complications attributed to AKI (Table 1.5). It currently remains uncertain whether the earlier initiation of RRT in critical illness before the onset of overt complications of AKI can improve outcomes. Accumulating evidence from observational pediatric studies demonstrate strong and consistent association between fluid accumulation at the time of RRT initiation and worse outcomes (59-62). Based on these findings, percent fluid overload (%FO) of higher than 10% should be considered when evaluating the timing for CRRT initiation. The formula used to calculate %FO is: [(Total fluid in – Total fluid out) / Admission weight * 100]. In adults, selected data from observational studies suggested early or pre-emptive RRT initiation may be associated with improved survival. However, three recent RCTs in adult critically ill patients showed conflicting results (63-65). These inconsistent findings will hopefully be further clarified with the completion of ongoing large multicenter RCTs.

The RRT modality most commonly used early in the course of hemodynamically unstable patients is continuous renal replacement therapy (CRRT). CRRT offers the advantages of adaptability to the patient condition, achievement of more consistent hemodynamic tolerance, and metabolic and fluid homeostasis. Although no definitive evidence has shown a survival advantage with one particular modality, recent data have suggested that initial support with CRRT may better facilitate recovery of kidney function to RRT independence and reduce the long-term risk of incident chronic kidney disease (66, 67). Earlier data suggested a potential benefit from higher-intensity dose RRT. However, subsequent evidence showed no incremental

benefit of higher-intensity compared to lower-intensity RRT, with fewer metabolic complications occurring in those receiving lower-intensity support (68, 69).

1.7 Thesis Objectives

AKI is common and increasingly encountered in critically ill children. The development of AKI is not a trivial complication. Accumulating data clearly show suboptimal short-term and poor long-term outcomes after an episode of AKI. Understanding the epidemiology of AKI in the pediatric population and identification of those at greatest risk is critical. The current evidence base is limited by number of factors: 1) Existing epidemiological pediatric studies have used diverse AKI definitions. It is still unclear to what extent the use of different definitions affects AKI description and its association with outcomes using larger database studies. 2) There are limited pediatric studies that have applied the recent KDIGO consensus criteria to describe the epidemiology and outcome of AKI in PICU. 3) Across recent studies, the use of urine output, which increases the sensitivity of AKI definitions, was not always integrated. 4) The majority of AKI studies in pediatric population were single center with relatively small numbers of children. 5) Moreover, some of the current studies were limited to intubated PICU patients and/or excluded postoperative cardiac patients, further limiting the generalizability of their findings. 6) Long term survival outcomes for pediatric AKI patients are inadequately described and underreported. 7) Fluid overload has been shown to play an important role in the pathophysiology of AKI. This relationship has not been thoroughly examined in pediatric AKI population. The concept of "fluid overload" is described in the literature using various definitions. Although some of the proposed definitions have shown strong correlation with outcomes, it is unclear how generalizable these findings are considering

limitations in study design, size and methodology, and variation in case-mix. There are concerns about potential discrepancy in fluid overload estimation contingent on the definition applied. Moreover, there is no clear consensus on how to precisely and reliably define fluid overload.

I aimed to address these knowledge gaps by conducting a large multicenter pediatric study inclusive of all PICU admissions in the province of Alberta. In addition, I performed a systematic review and meta-analysis to describe the methods used to measure fluid balance, define fluid overload, and evaluate the association between fluid balance and outcomes in critically ill children. The specific goals of my thesis included:

1. Describe the population-based incidence of acute kidney injury among critically ill children in Alberta using the KDIGO consensus criteria.
2. Evaluate the utility of KDIGO staging scheme in describing AKI and its association with outcome in PICU.
3. Characterize AKI in PICU and describe risk factors associated with acute kidney injury in critically ill children.
4. Describe the treatment intensity (ventilation, vasoactive support, renal replacement therapy), resource use (PICU stay, hospital stay), and mortality in critically ill children with AKI.
5. Describe the methods used to assess fluid balance and describe the definitions for fluid overload.
6. Evaluate the association between fluid balance and outcomes in critically ill children.

Table 1.1: KDIGO AKI Staging (2)

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline OR Increase of ≥ 0.3 mg/dl (≥ 26.5 mmol/l)	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase of ≥ 4.0 mg/dl (≥ 353.6 mmol/l) OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m^2	< 0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Table 1.2: The Renal Angina Index (RAI) to predict risk of AKI among critically ill children (16)

Risk Criteria			**Injury Criteria**		
Admission to ICU	1		Serum Creatinine	Fluid overload %	Score
Transplantation	3		No change	< 5	1
Ventilation, vasoactive support, or both	5	X	Increase >1-1.49 times	5-10	2
			Increase >1.5-1.99 times	11-15	4
			Increase ≥ 2 times	>15	8

The RAI calculation is assessed 12 h after a patient is admitted to an intensive care unit and used for prediction of severe acute kidney injury 72 h (3 days) later. The RAI is calculated by multiplying the patient risk score by the injury score (scores 1 to 40). The higher score for either of the injury criteria (Creatinine or fluid overload) is used. A RAI product of ≥ 8 fulfills the renal angina classification. Transplantation refers to solid organ or stem cell transplantation.

Table 1.3: Selected Epidemiological AKI Studies in Critically Ill Children

Study	**year**	**Population**	**n**	**AKI Definition**	**Cr /UOP criteria**	**AKI Incidence**
Plotz et al. (23)	2008	Intubated PICU	103	pRIFLE	Both	58%
Schneider et al. (24)	2010	General PICU	3396	RIFLE	Cr only	16%
Alkandri et al. (25)	2011	General PICU	2106	AKIN	Cr only	18%
Aydin et al (26)	2012	Post cardiac surgery	458	RIFLE	Cr only	51%
Soler at al. (27)	2013	General PICU	266	pRIFLE	Both	27%
Sanchez-Pinto et al. (29)	2015	General PICU	8260	KDIGO	Cr only	18%
Volpon et al (31)	2016	General PICU	160	pRIFLE, KDIGO	Both	46%
Blinder et al (32)	2017	Post cardiac surgery	799	AKIN	Cr only	36%
AWARE (33)	2017	General PICU	4683	KDIGO	Both	27%

Table 1.4: List of medications known to be associated with nephrotoxicity (Adopted from (18))

Acyclovir	Enalaprilat	Mesalamine
Ambisome	Foscarnet	Methotrexate
Amikacin	Gadopentetate dimegluminea	Nafcillin
Amphotericin B	Gadoxetate disodiuma	Piperacillin/tazobactam
Captopril	Ganciclovir	Piperacillin
Carboplatin	Gentamicin	Sirolimus
Cefotaxime	Ibuprofen	Sulfasalazine
Ceftazidime	Ifosfamide	Tacrolimus
Cefuroxime	Iodixano	Ticarcillin/clavulanic acid
Cidofovir	Iohexo	Tobramycin
Cisplatin	Iopamido	Topiramate
Colistimethate	Ioversol	Valacyclovir
Cyclosporine	Ketorolac	Valganciclovir
Dapsone	Lisinopril	Vancomycin
Enalapril	Lithium	Zonisamide

Table 1.5: Summary of classic and relative indications for initiation of RRT

Conventional ("Rescue") Indications
• Oliguria or anuria • Azotemia (serum urea > 36 mmol/L or uremic organ complications) • Metabolic acidosis/acidemia (pH <7.15) • Hyperkalemia (K+ >6.5 mEq/L and/or rapidly rising and/or cardiac toxicity) • Volume overload (clinically significant, diuretic unresponsive organ edema) • Sodium disorders (progressive and/or uncontrolled dysnatremia) • Overdose with dialyzable toxin • Refractory hyperammonemia • Thermoregulation (uncontrolled hyper or hypothermia)
Relative (Expanded) Indications
• Rapidly worsening AKI or illness severity in the setting of reduced renal reserve • Allow delivery of adequate nutritional support • Fluid removal or prevention of excessive fluid accumulation • Chemotherapy induced organ injury and/or transfusion support • Immuno-modulation and restoration of immune responsiveness in sepsis

CHAPTER 2

Epidemiology and Outcomes of Acute Kidney Injury in Critically Ill Children: A Population-Based Study

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2.1 Abstract

Background:

Acute kidney injury (AKI) is associated with greater risk of morbidity, mortality, and health services use for critically ill children. However, the precise characteristics and the incremental risks associated with AKI have not been described at a population-level.

Methods:

I conducted a population-based multicentre cohort study inclusive of all children admitted to three pediatric intensive care units (PICU) in Alberta, Canada between January 1 to December 31, 2015, utilizing prospectively collected data from a bedside clinical information system and data repository. AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) definition, using both serum creatinine and urine output criteria.

Findings:

A total of 1017 patients were included. AKI developed in 308 patients (30.3%; 95% CI, 28.1% to 33.8%) and severe AKI (KDIGO stage 2 and 3) developed in 124 patients (12.2%; 95% CI, 10.3% to 14.4%). Incidence rates for critical illness-associated AKI and severe AKI were 34 (95% CI, 30.3 to 38.0) and 14 (95% CI, 11.38 to 16.38) per 100,000 children-year, respectively. Severe AKI incidence rates were greater in males (Incidence Rate Ratio [IRR] 1.55; 95%, 1.08 to 2.33) and infants younger than one year of age (IRR 14.77, 95% CI 10.36 to 21.07). Thirty-two patients (3.1%) did not survive to PICU discharge. The AKI-associated PICU mortality rate was 2.3 (95% CI, 1.4 to 3.5) per 100,000 children-year. After adjustment for weight, case-mix, illness acuity (Pediatric Index of Mortality 3) and PICU site, severe AKI was associated with greater

PICU mortality (odds ratio [OR] 11.93; 95% CI, 4.68 to 30.42) and 1-year mortality (OR 5.50, 95% CI, 2.76 to 10.96). Severe AKI was further associated with greater duration of mechanical ventilation, duration of vasoactive support and lengths of PICU and hospital stay.

Interpretation:

The population-level burden of AKI and its attributable risks, including greater mortality and health services use, are considerable among critically ill children. These findings emphasize the need for enhanced surveillance for AKI, identification of modifiable risks and evaluation of interventional strategies.

2.2 Introduction

Acute kidney injury (AKI) occurring during critical illness is not a trivial complication. Accumulating data show poor outcomes after an episode of AKI, including greater risk of mortality, major morbidity and health services use (70). Understanding the epidemiology of AKI and its burden has been the focus of several pediatric studies; however, findings across these studies have been variable, mainly due to differences in study design, AKI definitions and cohort case-mix assessed. Few pediatrics studies have applied the recent Kidney Disease: Improving Global Outcomes (KDIGO) AKI consensus definition, though most have omitted the urine output criteria (28-30, 71). Recently, the Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults (AWARE) study, a large prospective multinational study, addressed many of these concerns and validated the utility of the KDIGO definition in diagnosing AKI and predicting its association with outcomes in critically ill children (33). In AWARE, AKI occurred in 27% and severe AKI in 12% of children, respectively. Mortality was highest among those with severe AKI and was further associated with greater use of mechanical ventilation and renal replacement therapy (RRT), and longer ICU stay.

The population-level incidence of AKI has yet to be described. Determination of the AKI incidence in critically ill children is important to establish its overall burden and optimally characterize those at greater risk. This is vital to enable devising preventative and therapeutic strategies. The objectives were to describe the population-based incidence, risk factors and outcomes associated with AKI in a large well-defined population.

2.3 Methods

The study was approved by the University of Alberta Health Research Ethics Board (REB File # PRO00063318). The need for written informed consent was waived.

2.3.1 Study population

This study was a retrospective population-based cohort study utilizing prospectively collected data on critically ill children in the province of Alberta, Canada. Alberta Health Services (AHS) provides all hospital care to the residents of Alberta (2015 population 4,177,527, of which 906,245 were children between 1 month and 17 year of age). Critically ill children in Alberta are managed in three university-affiliated multidisciplinary closed PICUs (two medical-surgical PICU and one cardiac PICU). The study population consisted of all children (1 month to 17 years) residing in Alberta admitted to any of the three PICUs between January 1 and December 31, 2015. Patients were excluded for any of the following: 1) presence of end-stage kidney disease (defined as glomerular filtration rate of less than 60 mL/min per 1.73 m2 for more than 3 months), 2) history of kidney transplant, 3) admission for less than 24 hours, and, 4) transfer into PICU from out of province. If a patient had more than one PICU admission during the study period, only the first admission was included.

2.3.2 Data collection

The data source was Alberta *eCritical* which is composed of a bedside clinical information system (MetaVision^{TM}, iMDsoft, Germany) and a data repository/clinical analytics system (TRACER) (72). MetaVision^{TM} provides full electronic inter-disciplinary clinical documentation and collation of demographic, diagnostic (i.e., comorbidity, diagnostic classification, surgical

status), laboratory and device data (i.e., monitor, ventilator, RRT). *eCritical* TRACER provides a comprehensive, multi-modal and integrated data repository of patient-specific ICU data enabling creation of reports and specific data extracts for administrative, quality, and research purposes. The *eCritical* platform functions within AHS, governed by a provincial multi-disciplinary executive leadership group. Data within *eCritical* systems undergo rigorous data quality assurance and audit (73). The size and demographics of the pediatric population in Alberta during the study period was obtained from Statistics Canada, a government agency commissioned with producing population related statistics (74).

Standard demographic and clinical data were retrieved. Demographic information included age, weight, sex, and date of admission. Severity of illness was assessed using Pediatric Index of Mortality 3 (PIM3) at admission (75). Seven main admission diagnostic criteria were assigned based on the primary admission diagnosis: shock, respiratory failure, central nervous system dysfunction, cardiac disease, post-surgery (non-cardiac) and trauma. Diagnoses that did not fit any of these categories were labeled "other". Co-morbidities including cancer, sepsis (defined as systemic inflammatory response syndrome plus proven or suspected infection), and history of previous bone marrow and solid organ transplant were recorded. Clinical data encompassed hourly fluid intake and output from all sources, receipt of non-invasive or invasive mechanical ventilation, infusions of vasoactive medications, or renal replacement therapy (RRT). All serum creatinine (SCr) values measured in the three months prior to and during PICU admission and index hospitalization were captured.

AKI was defined using Kidney Disease Improving Global Outcome (KDIGO) definition, utilizing both SCr and urine output criteria (2). When the two criteria resulted in different stages, the greater severity stage was used. Baseline SCr was defined as the lowest SCr in the 3 months preceding admission. When baseline SCr was unavailable, I used the average SCr norms for age and sex used in Alberta clinical laboratories (Appendix 2.1). In patients with no SCr measurements during PICU admission, only the urine output criteria were applied. If a patient had only one SCr value measured during PICU admission, the criteria of absolute SCr increase of ≥26.5 mmol/l was not applied. I defined severe AKI as KDIGO stage 2 and 3 based on prior pediatric studies showing these stages are associated with worse outcomes (22, 30, 33). Early AKI was defined as AKI occurring within the first 24 hours following PICU admission, while late AKI was defined as AKI occurring later in the PICU course after the first 24 hours. Fluid overload was defined as *peak* percent fluid overload more than 10% during the first 10 days of admission, calculated as follows:

(Cumulative daily fluid intake in liters – cumulative daily output in liters) / PICU admission weight in kilogram X 100%

2.3.3 Outcomes

The primary outcome was PICU mortality. Secondary outcomes included hospital and one-year mortality, duration of mechanical ventilation, duration of vasoactive support, receipt and duration of RRT, and length of PICU and hospital stay.

2.3.4 Statistical analysis

I performed descriptive statistics, reported for the whole cohort and stratified according to severe AKI status and PICU mortality. Categorical variables were reported as proportions and compared using bivariate logistic regression. For continuous variables, data are reported as medians with interquartile ranges (IQR) and compared using bivariate linear regression.

Population-based incidence and mortality rates were calculated using the pediatric population of Alberta in 2015 as denominator (74). Incidence rate ratio (IRR) was calculated for age and sex categories as follow: (Number of AKI cases in category/Number of category population in Alberta) / (Number of other pediatric AKI cases not in category/Number of Alberta children population not in category).

Multivariate logistic regression was used to identify factors independently associated with severe AKI. I included in the multivariate model variables carrying associations of $p < 0.10$ with severe AKI in the bivariate analysis, in addition to the pre-specified variables (weight, diagnosis, PIM3 score and site). To examine the association of severe AKI with outcomes, I used multivariate logistic and linear regression, as appropriate. I adjusted for the following pre-specified clinically important variables: weight, diagnosis, PIM3 score and site. Results are presented as odds ratios (ORs) with 95% confidence intervals (CI) for logistic regression and B regression coefficient with 95% CIs for linear regression. Finally, I performed survival analysis through 1-year using Cox proportional hazards regression adjusting for the same four variables (weight, diagnosis, PIM3 score and site) and reported hazard ratios with 95% CIs. Two-sided analyses were performed with p value of less than or equal to 0.05 considered to be statistically

significant. Analysis was performed using Stata version 15.1 (Stata Corp, College Station, TX, USA).

2.4 Results

During the 12-month study period, I analyzed data for 1,017 children who met the eligibility criteria (Figure 2.1). The rate of PICU admissions was 112 (95% CI, 105-119) per 100,000 children-year. The median (IQR) age was 24 (6.7-96.0) months and the median (IQR) weight was 12.7 (6.8-27.9) kg. Fifty-six percent were males. Details of baseline demographics and clinical characteristics are presented in Table 2.1.

2.4.1 Acute kidney injury incidence and risk factors

AKI occurred in 308 patients (30.3%; 95% CI, 28.1% to 33.8%) and severe AKI (stage 2 or 3) occurred in 124 patients (12.2%; 95% CI, 10.3% to 14.4%). The population incidence rates for critical illness-associated AKI and severe AKI were 34 (95% CI, 30 to 38) and 14 (95% CI, 11 to 16) per 100,000 children-year, respectively. Annual incidence rate for severe AKI was higher in males (Incidence Rate Ratio [IRR], 1.55; 95%, 1.08 to 2.33) compared to females and infants younger than one year of age compared to older children (IRR 14.77; 95% CI, 10.36 to 21.07) (Appendix 2.2).

Cardiac diagnosis was the most common diagnostic category in AKI patients, representing 41% of AKI patients and 43% of severe AKI patients. Although cardiac diagnosis was associated with severe AKI on bivariate analysis, this association did not persist on multivariate analysis. Factors associated with the development of severe AKI on multivariate analysis included PIM3 score, the receipt of vasoactive support, fluid overload and PICU site (Table 2.1). Fluid overload

occurred more frequently in those with severe AKI (50.8% vs 30.2%, p<0.001). Median (IQR) peak fluid overload % during the first 10 days was higher in those with severe AKI (9.4% [3.6-17.9] versus 5.7% [2.6-10.2], p<0.001).

2.4.2 Timing and characteristics of AKI

The majority of AKI cases (57.8%) were diagnosed during the first 24 hours of admission. Early AKI had higher proportion of severe AKI cases compared to AKI occurring later in the PICU course (50.6% vs 26.2%; p<0.001). Early AKI occurred more frequently in cardiac patients, while late AKI occurred more commonly in respiratory and post-surgical patients.

The average time to AKI resolution (based on SCr decreasing to <1.5 times baseline and urine output >0.5 ml/kg/hr for more than 12 hours) was 3.02 days (95% CI, 1.62-4.41). Both early and severe AKI were associated with longer duration of AKI (p<0.001) compared with late and stage 1 AKI. The diagnosis of the majority of AKI cases was made using the SCr criteria (145 cases, 47.1%), while 97 cases (31.5%) were diagnosed based on urine output criteria, and 66 cases (21.4%) met both urine and creatinine criteria (Figure 2.2). AKI based on both criteria was more severe and of longer duration compared to AKI diagnosed based on one criteria (p<0.001). In early AKI, the majority of cases (55%) were diagnosed based on the SCr criteria, while in late AKI, most cases (52%) were diagnosed based on urine output criteria. Detailed data of AKI characteristics and timing are provided in the Appendix.

In patients with no measured SCr during PICU admission (18.7% of the cohort), AKI was diagnosed less frequently compared to those with at least one creatinine measurement (8.4%

versus 35.3%, p <0.001). PIM3 scores (median [IQR]) were lower in patients with no measured SCr (-6.15 [-6.51 to -4.93] vs -4.51 [-5.60 to -3.89], p<0.001).

Baseline SCr was unavailable and was estimated for 49.4% of children. AKI occurred less commonly in those without baseline SCr compared to those with available baseline SCr (21% vs 40%, p<0.001). Similar findings were observed in sensitivity analysis including only those children younger than 1 year of age. When omitting all patients with no baseline SCr, the incidence of AKI increased to 39.6%.

Twenty-one AKI patients (2.1%) received RRT with 17 patients treated with continuous RRT and 4 with peritoneal dialysis.

2.4.3 AKI association with mortality

Thirty-two patients (3.1%) died during PICU admission, and of those 21 (65%) had AKI. The annual AKI-associated PICU mortality rate was 2.3 (95% CI, 1.4-3.5) per 100,000 children. AKI-associated PICU mortality rate was higher in infants younger than 1 year of age compared to older children (IRR 13.87, 95% CI, 5.89-32.67). There was no significant difference in mortality risk between males and females (Appendix 2.13).

When comparing survivors and non-survivors, those who died had a higher PIM3 score, were more likely to have >10% fluid overload, and receive treatment with mechanical ventilation, vasoactive support and RRT (Table 2.2).

Patients with AKI had higher mortality rates compared to patients with no AKI (6.8% vs 1.1%; OR 4.64; 95% CI, 2.21-9.75). There was gradient increase in mortality rates according to increasing AKI severity, however only stage 2 and stage 3 AKI were associated with PICU mortality. Severe AKI conferred an incremental risk of PICU mortality after adjustment for weight, diagnosis, PIM3 score, and PICU site (adjusted-odds ratio [aOR] 11.93; 95% CI, 4.68-30.42).

Mortality rates did not differ between those with estimated baseline SCr and measured baseline SCr (2.7% vs 3.4%, p=0.52). However, patients with no measured SCr during admission had significantly lower mortality rates compared to those with at least one measured SCr (0.5% vs 3.8%, p=0.02).

Thirty-eight patients (3.7%) died before hospital discharge and 56 (5.5%) died within one year of PICU admission. Post-discharge mortality (n=18) were higher in patients with severe AKI (OR 2.84, 95% CI 1.04-7.81). In adjusted analysis, severe AKI was associated with greater hospital (OR 9.20; 95% CI, 4.00-21.19) and 1-year mortality (OR 5.50, 95% CI, 2.76-10.96). Cox proportional hazards analysis, adjusting for the same variables, showed that stage 2 and stage 3 AKI were significantly associated with 1-year mortality (Figure 2.3).

2.4.4 AKI association with other outcomes

In adjusted analyses, patients with severe AKI received longer duration of mechanical ventilation (3.31 days, 95% CI, 1.06-5.55) and vasoactive therapy (2.46 days; 95% CI, 1.44-

3.48). In addition, patients with severe AKI stayed longer in PICU (3.75 days; 95% CI, 1.28-6.23) and hospital (12.09 days; 95% CI 3.11-21.06) (Table 2.3).

2.5 Discussion

This large multicenter cohort study described the population-level epidemiology and outcomes for critically ill children with AKI. AKI was common, occurring in an estimated 30% of the PICU patients, with annual incidence rate of 34 per 100,000 children. Severe AKI was independently associated with greater risk of short and longer-term mortality and other important secondary outcomes, including longer receipt of mechanical ventilation and vasoactive support, and prolonged PICU and hospital stay.

To my knowledge, no pediatric study has described the population-level incidence of AKI among critically ill children. The incidence rate of AKI in this study population was higher in comparison to other acute illnesses associated with PICU admission such as respiratory failure (32 per 100,000 person-year), cardiac diseases (23 per 100,000 person-years), shock (8 per 100,000 person-years), and trauma (7 per 100,000 person-years). In adult populations, the incidence rate of AKI among critically ill patients was estimated at 180 per 100,000 person-years (21), with 58% of adult ICU patients developing AKI (22). Several hospital-based pediatric studies, applying different AKI definitions, have described the incidence rates of AKI between 16-58% (24, 25, 27, 28, 30, 33). The AWARE study prospectively evaluated the epidemiology of AKI in a large pediatric population from 32 PICUs from around the world using the KDIGO definition (33). Remarkably, the incidence and associated outcomes of AKI in this study were similar to those described in AWARE. In both studies, there was step-wise increase in mortality

associated with worsening AKI severity. This consistency in findings between the two studies extends confidence in the estimates reported in AWARE and suggests that KDIGO criteria is robust for discriminating clinically relevant outcomes in pediatric populations. In addition to greater risk for mortality, I found severe AKI to be associated with greater health services use. These results have significant implications on health care delivery, especially in areas with limited resources, and further highlights the need for effective strategies to identify, prevent and mitigate the impact of AKI.

The long-term implications of AKI have seldom been described in children surviving critical illness, with most pediatric AKI studies only reporting mortality at PICU or hospital discharge. In this study, severe AKI patients were at increased risk of death beyond discharge from hospital, adding to the overall burden potentially attributable to AKI. A recent retrospective study including over 2,000 PICU patients found AKI to be associated with 5-year mortality (76). This finding is consistent with data from numerous adult studies showing AKI to have negative impact on long-term survival (77-79).

The majority of AKI cases occurred early following PICU admission, a pattern that has been described in earlier AKI studies (25). This observation emphasizes the importance of surveillance for AKI occurring at or early after PICU admission. Approximately one-third of AKI patients were diagnosed based on urine output criteria alone, underscoring the importance of closely monitoring urine output during PICU stay. Similar to findings in AWARE, in this study, approximately half of AKI cases diagnosed after the first 24 hours of PICU admission would have been missed if urine output data were not evaluated (33).

The findings show that critically ill children who are younger than 1 year to be at higher risk of developing AKI and may represent a future target population for greater surveillance, earlier intervention or the focus of preventive strategies. In addition, the study identified three clinical factors associated with the development of severe AKI including severity of illness, the receipt for vasoactive support and fluid overload. Of these, fluid overload may be potentially modifiable and a target for interventional strategies. The study findings align with robust evidence describing the negative association between fluid accumulation and patient outcomes, including AKI (80). Limited evidence has assessed strategies to prevent and mitigate fluid accumulation in patients with or at risk of AKI (49, 81). The findings suggest that future research should now evaluate potential interventions to prevent and reduce avoidable fluid accumulation in critically ill children.

The study is strengthened by the use of pre-specified protocol and the utilization of prospectively electronically collected data with no missing data points. The data were obtained from 3 different PICUs with variable practices and processes of care increasing the generalizability of the findings. The population-based nature and inclusion of all patients in a geographically defined area governed by a single health system minimizes the risk of selection bias while providing robust estimates of disease burden. Moreover, unlike prior work, this study was able to evaluate patients for AKI during the entire PICU stay. The study also described long-term outcome data, which have been infrequently reported in pediatric AKI literature.

The study has limitations that warrant discussion. The study is observational in design and as such I cannot definitively confirm the causal relationship between AKI and clinical outcomes. The population-based incidence of all pediatric AKI cases occurring in hospital cannot be determined, considering I only included patients admitted to PICU. Despite adjusting for severity of illness and other important potential confounders, the retrospective design limited the ability to account for important interventions such as exposure to nephrotoxins or the use of diuretics. This could partly explain the observed variable AKI incidence between centres. The baseline SCr was not known in about half of the patients. Similar figures have been described in other pediatric studies and can be explained by the fact that majority of children have no comorbidities that necessitate evaluating SCr in the community (6, 15). Nevertheless, this could be a source of classification bias. When I excluded those patients, the incidence of AKI was higher but the association with mortality was unchanged. Finally, the fluid deficit state and fluid given prior to PICU admission were not available for the calculations of fluid overload, which might have resulted in misclassification.

2.6 Conclusion

In summary, AKI is common in critically ill children and portends worse outcomes, including greater mortality and health care resource utilization. AKI therefore represents an important burden for health care. The findings of this study highlight the need for improved detection of AKI and for efforts to improve care for these patients.

Table 2.1: Characteristics of Study Population Stratified by Severe AKI

Variables	All patients (N=1017)	No Severe AKI (N=893)	Severe AKI (N=124)	OR (95% CI)	Adjusted OR (95% CI)
Male - no (%)	575 (56.6)	498 (55.8)	77 (62.1)	0.77 (0.52 – 1.13)	
Age (month)	24.0 (6.7- 96.0)	24.0 (6.97-96.0)	24.0 (4.68 – 108.0)	0.99 (0.99 – 1.00)	
Weight (kg)	12.7 (6.8 – 27.9)	12.70 (6.90-27.0)	12.50 (5.65-34.60)	1.00 (0.99 – 1.01)	
PIM 3 score	-4.80 (-6.1 to – 4.1)	-4.94 (-6.23 to -4.22)	-4.13 (-4.45 to -3.31)	1.72 (1.49 – 1.99) *	1.23 (1.01 – 1.50) *
Site- no. (%) Site 1 Site 2 Site 3	 339 (33.3) 183 (18.0) 495 (48.7)	 291 (32.6) 131 (14.67) 471 (52.7)	 48 (38.7) 52 (41.9) 24 (19.4)	 Reference 2.40 (1.54 – 3.75) * 0.31 (0.19 – 0.51) *	 0.30 (0.17 – 0.53) *
Diagnosis - no. (%) Shock Respiratory Central nervous system Cardiac Post-surgery Trauma Other	 75 (7.4) 289 (28.4) 100 (9.8) 210 (20.7) 220 (21.6) 67 (6.6) 56 (5.5)	 57 (6.4) 274 (30.7) 94 (10.5) 157 (17.6) 213 (23.9) 56 (6.3) 42 (4.7)	 18 (14.5) 15 (12.1) 6 (4.8) 53 (42.7) 7 (5.7) 11 (8.9) 14 (11.3)	 2.49 (1.41 – 4.39) * 0.31 (0.18 – 0.54) * 0.43 (0.18 – 1.01) 3.50 (2.36 – 5.20) * 0.19 (0.08 – 0.42) * 1.45 (0.74 – 2.86) 2.58 (1.36 – 4.87) *	
Sepsis- no. (%)	67 (6.6)	51 (5.7)	16 (12.9)	2.45 (1.34 – 4.44) *	
Oncological diagnosis – no. (%)	24 (2.4)	20 (2.2)	4 (3.2)	1.45 (0.49 – 4.33)	
History of transplantation - no. (%)	15 (1.5)	10 (1.1)	5 (4.0)	3.71 (1.25 – 11.04) *	
Cardiopulmonary bypass- no. (%)	104 (10.2)	76 (8.5)	28 (22.9)	3.14 (1.94 – 5.08) *	
Peak FO% >10%	333 (32.7)	270 (30.2)	63 (50.8)	2.38 (1.63 – 3.48) *	2.13 (1.35 – 3.37) *
Mechanical Ventilation- no (%)	431 (42.4)	345 (38.6)	86 (69.4)	3.59 (2.40 – 5.39) *	
Non-invasive ventilation- no (%)	134 (13.2)	112 (12.5)	22 (17.7)	1.50 (0.91 – 2.48)	
Vasoactive support – no (%)	229 (22.5)	150 (16.8)	79 (63.7)	8.69 (5.79 – 13.05) *	4.35 (2.51– 7.54) *

(* p <0.05%)

Table 2.2: Characteristics of Study Population Stratified by PICU mortality

Variables	All patients (N=1017)	Survivors (N= 985)	Non-survivors (N=32)	OR (95% CI)
Male- no (%)	575 (56.6)	557 (56.5)	18 (56.3)	1.0 (0.48 – 2.1)
Age (month)	24.0 (6.7- 96.0)	24.0 (6.7 – 96.0)	24.0 (7.2– 60.0)	0.99 (0.99-1.00)
Weight (kg)	12.7 (6.8 – 27.9)	12.7 (6.8 – 28.1)	13.35 (8.4 –20.0)	0.99 (0.97 - 1.0)
PIM 3 score	-4.8 (-6.1 to – 4.1)	-4.8 (-6.1 to -4.2)	-3.2 (-4.4 to -2.1)	2.35 (1.80 – 3.06) *
Site- no. (%)				
Site 1	339 (33.3)	322 (32.7)	17 (53.1)	Reference
Site 2	183 (18.0)	180 (18.3)	3 (9.4)	0.32 (0.09 – 1.09)
Site 3	495 (48.7)	483 (49.0)	12 (37.5)	0.47 (0.22 – 1.00)
Diagnosis - no. (%)				
Shock	75 (7.4)	68 (6.9)	7 (21.9)	3.78 (1.58 – 9.04) *
Respiratory	289 (28.4)	282 (28.6)	7 (21.9)	0.70 (0.30 – 1.63)
Central nervous system	100 (9.8)	98 (10.0)	2 (6.3)	0.60 (0.14 – 2.56)
Cardiac	210 (20.7)	205 (20.8)	5 (15.6)	0.70 (0.27 – 1.85)
Post-surgery	220 (21.6)	218 (22.1)	2 (6.2)	0.23 (0.06 – 0.99) *
Trauma	67 (6.6)	58 (6.0)	9 (28.1)	6.25 (2.76 – 14.13) *
Other	56 (5.5)	56 (5.7)	0 (0)	N/A
Sepsis- no. (%)	67 (6.6)	63 (6.4)	4 (12.5)	2.09 (0.71 – 6.14)
Oncological diagnosis – no. (%)	24 (2.4)	22 (2.2)	2 (6.25)	2.92 (0.66 – 12.98)
History of transplantation -no. (%)	15 (1.5)	14 (1.4)	1 (3.1)	2.24 (0.29 – 17.55)
Cardiopulmonary bypass- no. (%)	104 (10.2)	103 (10.4)	1 (3.1)	0.28 (0.04 – 2.04)
Maximum stage of AKI- no (%)				
No AKI	709 (69.7)	698 (70.9)	11 (34.4)	Reference
Stage 1	184 (18.1)	181 (18.3)	3 (9.3)	1.05 (0.29 – 3.81)
Stage 2	79 (7.8)	73 (7.4)	6 (18.8)	5.22 (1.87– 14.51) *
Stage 3	45 (4.4)	33 (3.6)	12 (37.5)	23.07 (9.48 –56.16) *
Any AKI	308 (30.3)	287 (29.1)	21 (65.6)	4.64 (2.21 – 9.75) *
Severe AKI (stage 2 or 3)	124 (12.2)	106 (10.8)	18 (56.3)	10.66 (5.15- 22.06) *
Peak FO% during first 10 days	5.86 (2.63 – 11.02)	5.74 (2.58 – 10.68)	15.15 (8.71-34.87)	1.08 (1.06 – 1.1) *
Peak FO% >10%- no. (%)	333 (32.7)	310 (31.5)	23 (71.9)	5.56 (2.55 – 12.17) *
Mechanical Ventilation- no (%)	431 (42.4)	400 (40.6)	31 (96.8)	45.34 (6.16 – 333.46) *
Non-invasive ventilation- no (%)	134 (13.2)	129 (13.1)	5 (15.6)	1.23 (0.46 – 3.25)
Renal replacement therapy- no (%)	25 (2.5)	16 (1.6)	9 (28.1)	23 .70 (9.49 – 59.19) *
Vasoactive support – no (%)	229 (22.5)	202 (20.5)	27 (84.4)	20.93 (7.96 – 55.03) *

(* p <0.05%)

Table 2.3: Severe AKI Association with Outcomes

Variables	OR or B Coefficient (95% CI)	Adjusted OR or B Coefficient (95% CI)
PICU Mortality	10.66 (5.15–22.06)	11.93 (4.68–30.42)
Hospital Mortality	9.91 (5.03–19.52)	9.20 (4.00–21.19)
1-year Mortality	7.52 (4.24–13.36)	5.50 (2.76–10.96)
PICU LOS (days)	*B*=4.97 (2.58–7.37)	*B*=3.75 (1.28–6.23)
Hospital LOS (days)	*B*=18.47 (9.84–27.04)	*B*=12.09 (3.11–21.06)
Length of Mechanical ventilation (days)	*B*=4.09 (1.94–6.23)	*B*=3.31 (1.06–5.55)
Length of inotrope use (days)	*B*=3.37 (2.40–4.34)	*B*=2.46 (1.44–3.48)

Reported as odds ratio (95% CI) or *B* regression coefficient (95% CI)
Adjusted for weight, site, diagnosis and PIM3
All $p < 0.05$

Figure 2.1: Diagram on Patient Inclusion, AKI Incidence, and Outcomes

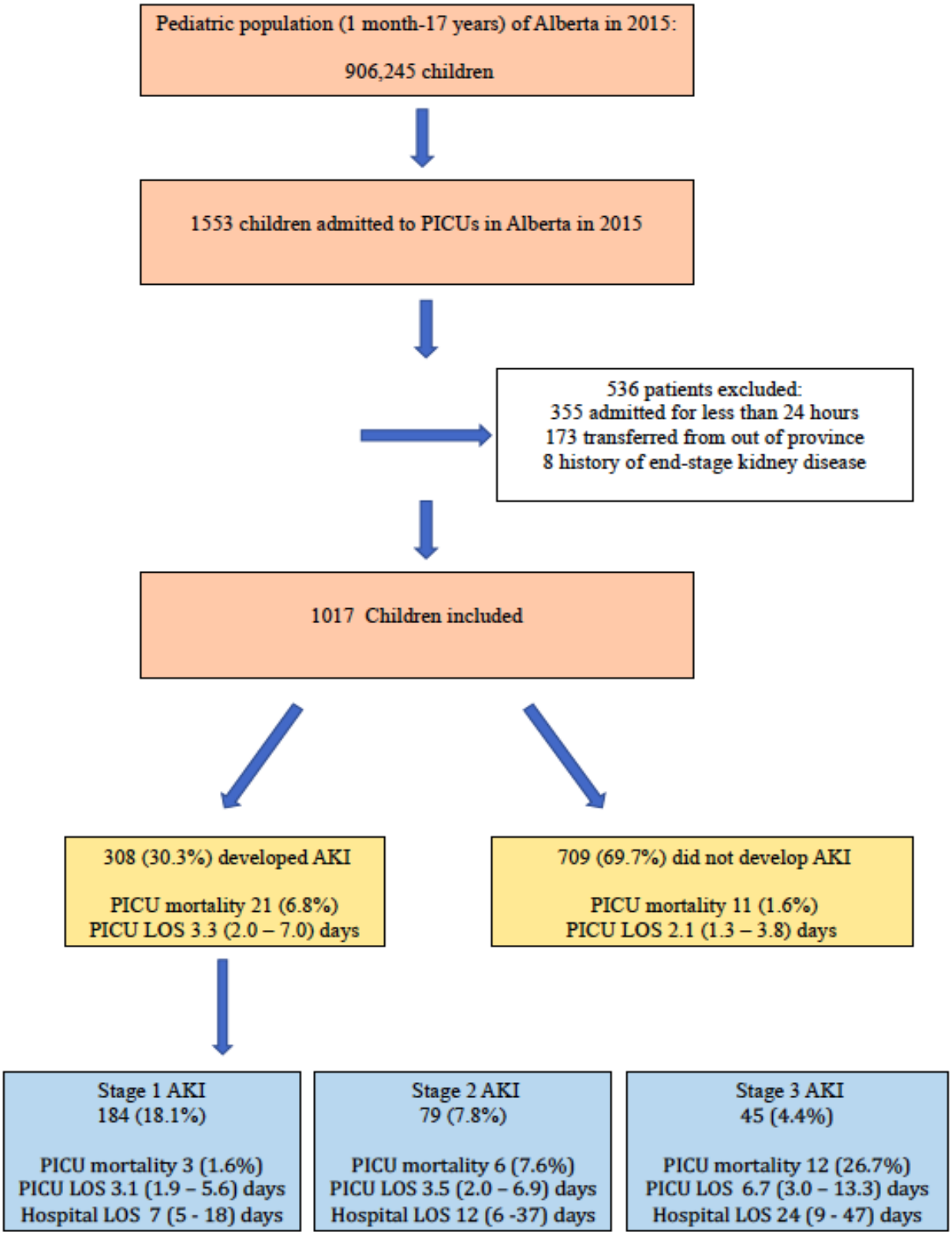
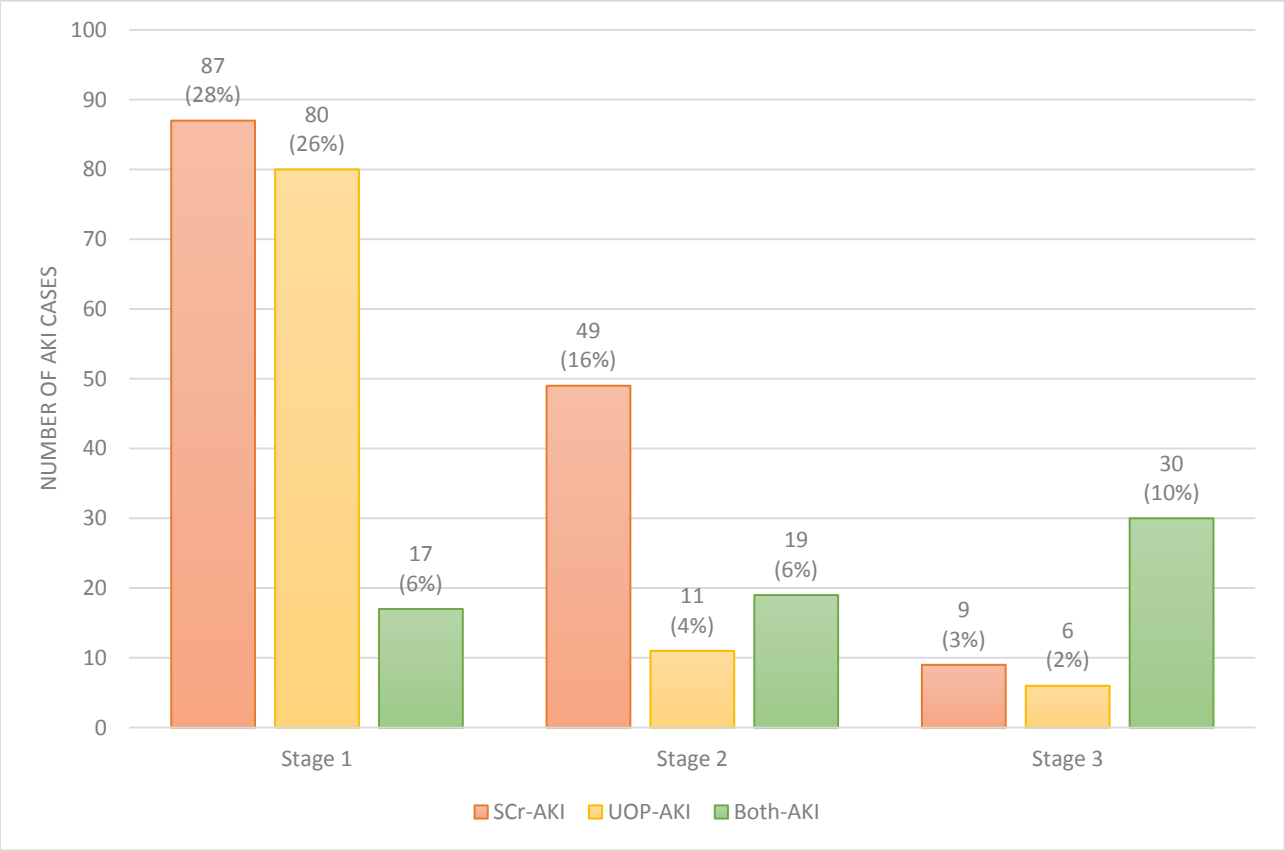
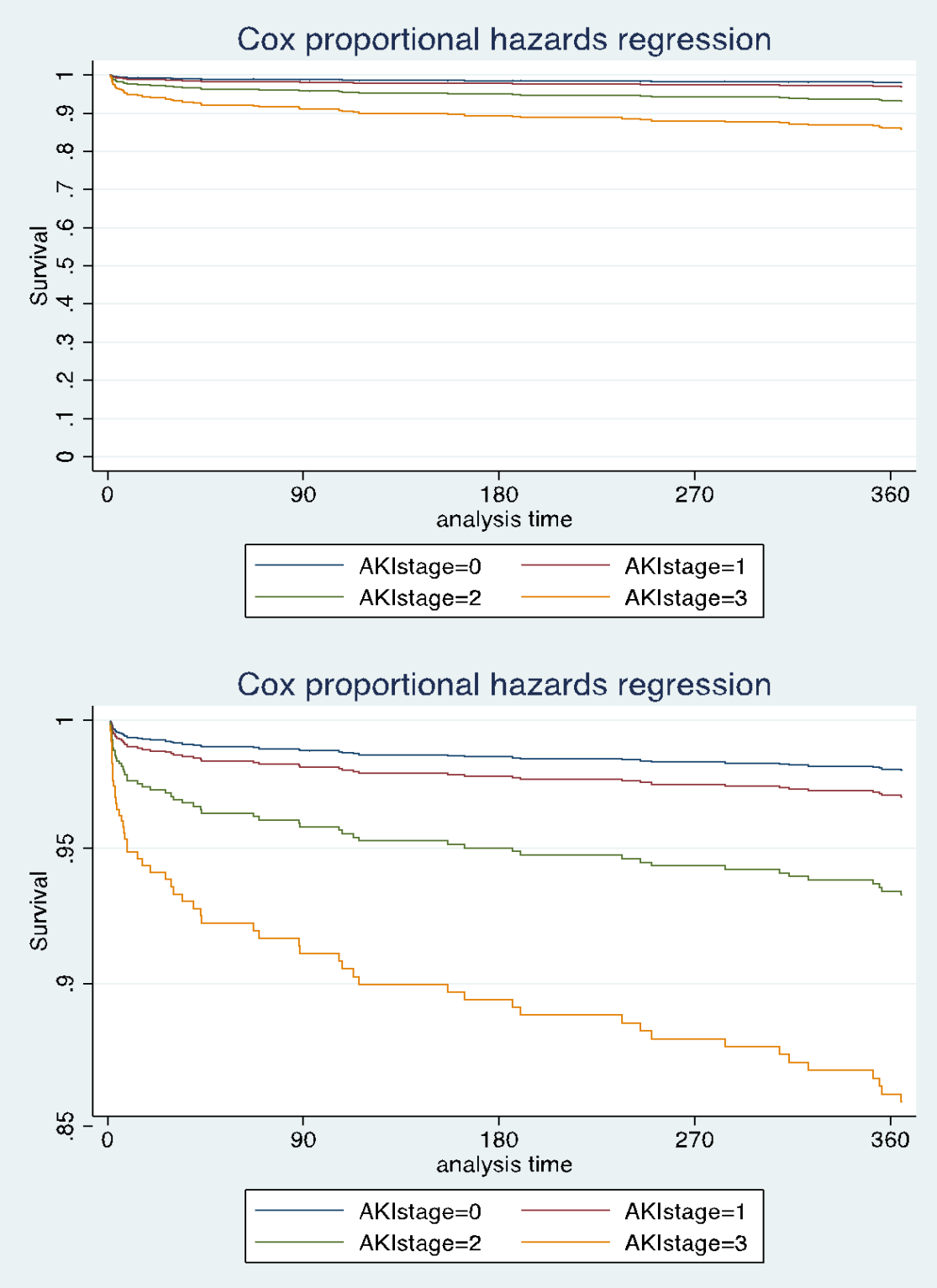


Figure 2.2: Number and Percentage of AKI Cases According to Definition Criteria Used in Diagnosis



SCr-AKI: AKI diagnosed after meeting the serum creatinine criteria only.
UOP-AKI: AKI diagnosed after meeting the urine output criteria only.
Both-AKI: AKI diagnosed after meeting both diagnostic criteria.

Figure 2.3: Adjusted One-year Survival Analysis Using Cox Proportional Hazards Regression



Number at Risk

	0	90 days	180 days	270 days	360 days
No AKI	709	698	695	693	687
Stage 1	184	180	177	175	174
Stage 2	79	70	69	68	68
Stage 3	45	32	32	32	32

AKI Stage	Hazard Ratio	95% Confidence Interval
Stage 1	1.54	0.67 to 3.45
Stage 2	3.50	1.57 to 7.81
Stage 3	7.67	3.66 to 16.10

2.7 Appendix

Appendix 2.1: The Average SCr Norms for Age and Sex in Alberta Clinical Laboratories (in μmol/L)

Age	Male	Female
0-23 months	10-40	10-40
2-5 years	20-45	20-45
6-12 years	20-75	20-75
13-14 years	30-95	30-95
15-150 years	40-100	50-120

Source:
https://www.albertahealthservices.ca/webapps/labservices/index.asp?id=230&tests=&zoneid=1&details=true

Appendix-Table 2.2: Annual Incidence Rates for AKI and Severe AKI

1) Stratified by age-group for AKI

Age category	AKI cases	Population size	Annual incidence (per 100,000)	Incidence Rate Ratio (95% CI)
Less than 1 year	129	55,714	232	11.0 (8.77 – 13.80)
1-4 years	51	214,647	24	0.64 (0.47 – 0.86)
5-9 years	36	261,001	14	0.32 (0.23 – 0.46)
10-14 years	54	232,620	23	0.62 (0.46 – 0.83)
15-17 years	38	142,263	27	0.76 (0.54 – 1.06)
1 mon – 17 yrs	308	906,245	34	

2) Stratified by age-group for severe AKI

Age category	Severe AKI cases	Population size	Annual incidence (per 100,000)	Incidence Rate Ratio (95% CI)
Less than 1 year	60	55,714	108	14.77 (10.36 – 21.07)
1-4 years	22	214,647	10	0.69 (0.44 – 1.10)
5-9 years	13	261,001	5	0.30 (0.16 – 0.51)
10-14 years	18	232,620	8	0.49 (0.30 – 0.81)
15-17 years	11	142,263	8	0.52 (0.28 - 0.97)
1 mon-17 yrs	124	906,245	14	

3) Stratified by gender for AKI

	AKI cases	Population size	Annual incidence (per 100,000)	Relative Risk (95% CI)
Male	170	465,058	37	1.17 (0.93 – 1.46)
Female	138	441,187	31	
All	308	906,245	34	

4) Stratified by gender for severe AKI

	Severe AKI cases	Population size	Annual incidence (per 100,000)	Relative Risk (95% CI)
Male	77	465,058	17	1.55 (1.08 – 2.33)
Female	47	441,187	11	
All	124	906,245	14	

Appendix 2.3: Timing of AKI Onset

Day	Number of AKI cases	% of AKI Cases	Cumulative AKI Incidence (%)
1	178	57.8 %	178 (57.8%)
2	74	24.0 %	252 (81.8%)
3	20	6.5 %	272 (88.3%)
4	11	3.6 %	283 (91.9%)
5	9	2.9 %	292 (94.8%)
6	4	1.3 %	296 (96.1%)
7	3	1.0 %	299 (97.1%)
8	2	0.6 %	301 (97.7%)
9	0	0 %	301 (97.7%)
Day 10 and after	7	2.3 %	308 (100%)
Total	308	100 %	

	Number of AKI Cases	% of AKI Cases
Early AKI (first 24 hours)	178	57.8%
Late AKI (after 24 hours)	130	42.2%

Appendix 2.4: AKI Severity According to Timing of Onset

	Severe	Not severe	OR (95% CI)
Early AKI	90	88	Reference
Late AKI	34	96	0.84 (0.71 to 0.98), p = 0.03

Appendix 2.5: AKI Duration (days) Stratified by Timing of Onset

	Mean	95% CI	B coefficient (95% CI)
Early AKI	2.44	2.10 – 2.77	Reference
Late AKI	1.49	1.30 – 1.68	-0.96 (-1.37 to - 0.52) $p < 0.001$

Appendix 2.6: AKI case-mix According to Timing of Onset

Diagnosis category	Early AKI	Late AKI	Total	OR (95%)
Shock	20 (11%)	11 (8%)	31	1.37 (0.64 – 2.92)
Respiratory	21 (12%)	30 (23%)	51	0.46 (0.24 – 0.82) *
Central nervous system	8 (4%)	9 (7%)	17	0.63 (0.24 – 1.63)
Cardiac	83 (47%)	44 (34%)	127	1.71 (1.10 – 2.72) *
Post-surgery	13 (7%)	20 (15%)	33	0.43 (0.21 – 0.90) *
Trauma	10 (6%)	9 (7%)	19	0.80 (0.32 – 2.00)
Other	23 (13%)	7 (5%)	30	2.60 (1.11 – 6.13) *
Total	178	130	308	

*P < 0.05

Appendix 2.7: Number of Cases According to Definition Criteria Used in AKI Diagnosis

Stage	Both Criteria	SCr-AKI	U-AKI
1	17	87	80
2	19	49	11
3	30	9	6
Total	66 (21%)	145 (47%)	97 (32%)

SCr-AKI: AKI diagnosed based on serum creatinine criteria
U-AKI: AKI diagnosed based on urine output criteria

Appendix 2.8: AKI Cases Association with Outcomes According to Definition Criteria Used in Diagnosis

[presented as count (percentage) and means (95% CI) with odds ratio (OR) and mean difference (MD), as appropriate]

	Both Criteria	SCr-AKI	UOP-AKI
PICU Mortality	12 (18.2%)	7 (4.8%)	2 (2.1%)
	Reference	OR 0.23 (0.09 – 0.61)	OR 0.09 (0.02 – 0.44)
PICU LOS (days)	13.2 (7.0 – 19.5)	4.6 (3.6 – 5.7)	9.6 (5.4 – 13.8)
	Reference	MD -8.60 (-13.68 to -3.52)	MD -3.63 (-9.08 to 1.83)
Receipt of Mechanical Ventilation	54 (81.8%)	89 (61.4%)	47 (48.5%)
	Reference	OR 0.35 (0.17 – 0.72)	OR 0.21 (0.10 – 0.44)
Receipt of Vasoactive Support	47 (71.2%)	78 (53.8%)	19 (19.6%)
	Reference	OR 0.47 (0.25 – 0.88)	OR 0.09 (0.05 – 0.20)
Renal Replacement Therapy	18 (27.2%)	2 (1.4%)	2 (2.1%)
	Reference	0.03 (0.01 – 0.17)	0.06 (0.01 – 0.25)

Appendix 2.9: Severity of AKI According to Criteria Used in Diagnosis

	Not severe AKI	Severe AKI	Total	OR (95%)
Both Criteria	17 (25.7 %)	49 (74.4 %)	66	Reference
SCr-AKI	87 (60 %)	58 (40%)	145	0.23 (0.12 – 0.44) p <0.001
UOP-AKI	80 (82.5 %)	17 (17.5 %)	97	0.07 (0.03 – 0.16) p <0.001

SCr-AKI: AKI diagnosed based on serum creatinine criteria
U-AKI: AKI diagnosed based on urine output criteria

Appendix 2.10: AKI Duration (days) According to Criteria Used in Diagnosis

	Mean	95% CI	Mean Difference (95% CI)
Both Criteria	3.47	2.75- 4.19	Reference
SCr-AKI	2.01	1.77 - 2.25	-1.46 (-1.96 to -0.95) p <0.001
UOP-AKI	1.10	1.02- 1.18	-2.36 (-2.91 to -1.82) p <0.001

SCr-AKI: AKI diagnosed based on serum creatinine criteria
U-AKI: AKI diagnosed based on urine output criteria

Appendix 2.11: Timing of AKI Incidence According to Criteria Used in Diagnosis

	Early AKI	Late AKI	Total	OR (95%)
Both Criteria	49 (74.2%)	17 (25.8)	66	2.52 (1.38 – 4.60) p < 0.001
SCr-AKI	99 (68.2%)	46 (31.7%)	145	2.29 (1.44 – 3.64) p < 0.001
UOP-AKI	30 (30.9%)	67 (69.1%)	97	0.19 (0.11 – 0.32) p < 0.001
Total	178	130	308	

SCr-AKI: AKI diagnosed based on serum creatinine criteria
U-AKI: AKI diagnosed based on urine output criteria

Appendix 2.12: AKI Case-mix According to Criteria Used in Diagnosis

Diagnosis category	Both Criteria	SCr-AKI	U-AKI	Total
Shock	9 (29.0%)	20 (64.5%)	2 (6.5%)	31
Respiratory	8 (15.7%)	9 (17.17%)	34 (66.8%)	51
Central nervous system	1 (5.9%)	6 (35.3%)	10 (58.8%)	17
Cardiac	36 (28.4%)	71 (55.9%)	20 (15.8%)	127
Post-surgery	3 (9.1%)	10 (30.3%)	20 (60.6%)	33
Trauma	4 (21.1%)	9 (47.4%)	6 (31.6%)	19
Other	5 (16.7%)	20 (66.8%)	5 (16.8%)	30
Total	66	145	97	308

P < 0.001

Appendix 2.13: Annual Mortality Rates for AKI

1) Comparing age-groups

Age category	AKI Mortality cases	Population size	Annual mortality rate (per 100,000)	Incidence Rate Ratio (95% CI)
Less than 1 year	10	55,714	17.9	13.87 (5.89 – 32.67)
1-4 years	5	214,647	2.3	1.40 (0.51 - 3.82)
5-9 years	3	261,001	1.1	0.41 (0.12 – 1.40)
10-14 years	2	232,620	0.9	0.30 (0.71- 1.31)
15-17 years	1	142,263	0.8	0.26 (0.04 – 2.00)
1 mon – 17 yrs	21	906,245	2.3	

2) Comparing gender

	AKI mortality cases	Population size	Annual mortality rate (per 100,000)	Incidence Rate Ratio (95% CI)
Male	12	465,058	2.6	1.26 (0.53 – 3.00)
Female	9	441,187	2.0	
All	21	906,245	2.3	

CHAPTER 3

Associations Between Fluid Balance and Outcomes in Critically Ill Children: A Protocol for a Systematic Review and Meta-Analysis

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ABSTRACT

Background:

Fluid therapy is a mainstay during the resuscitation of critically ill children. After initial stabilization, excessive fluid accumulation may lead to complications of fluid overload, which has been independently associated with increased risk for mortality and major morbidity in critically ill children.

Objectives:

Perform an evidence synthesis to describe the methods used to measure fluid balance, define fluid overload, and evaluate the association between fluid balance and outcomes in critically ill children.

Design:

Systematic review and meta-analysis.

Measurements:

Fluid balance, fluid accumulation, and fluid overload as defined by authors.

Methods:

We will search Ovid MEDLINE, Ovid EMBASE, Cochrane Library, and ProQuest, Dissertations and Theses. In addition, we will search www.clinicaltrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the proceedings of selected key conferences for ongoing and completed studies. Search strategy will be done in

consultation with a research librarian. Clinical trials and observational studies (from database inception to present) in patients (<25 years) admitted to pediatric intensive care units (PICUs) reporting fluid balance, fluid accumulation, or fluid overload, and associated outcomes will be included. Language will not be restricted. Two reviewers will independently screen studies and extract data. Primary outcome is mortality, and secondary outcomes encompass critical care resource utilization. Quality of evidence and risk of bias will be assessed using the Newcastle-Ottawa Scale (NOS). Results will be synthesized qualitatively and pooled for meta-analysis if possible.

Limitations:

Quality of the included studies; lack of randomized trials; high degrees of expected heterogeneity; and variations in definitions of fluid balance and fluid overload between studies.

Conclusion:

We will comprehensively appraise and summarize the evidence of the association between fluid balance and outcomes in critically ill children, and in doing so attempt to harmonize definitions related to fluid balance, accumulation, and overload.

Systematic review registration:

PROSPERO: CRD42016036209.

Keywords:

fluid balance, fluid overload, resuscitation, pediatric, critical illness, mortality

What was known before:

Positive fluid balance is common in critically ill children and independently associated with worse outcomes.

What this study adds:

This systematic review will comprehensively appraise and summarize the evidence evaluating the association between fluid balance and outcomes in critically ill children.

3.1 Background

Fluid therapy is the cornerstone of resuscitation in critically ill children. Reestablishment of adequate intravascular volume using early aggressive fluid administration is lifesaving (82-84). Moreover, beyond fluid therapy directed at resuscitation, critically ill children often receive variable amounts of obligatory fluid intake (ie, medications, nutrition, transfusions) (85, 86). This cumulative fluid delivery often exceeds net fluid loss, leading to a positive fluid balance. Growing body of circumstantial evidence suggests that the accumulation of fluid beyond the initial resuscitation phase may exert an incremental risk for major morbidity and mortality (85-91). These observations highlight the importance of monitoring fluid status and evaluating for the degree of fluid accumulation. As a consequence, fluid balance is routinely measured in critically ill children using several methods such as recorded daily intake-output and serial body weight measurements. However, the precision of such methods in accurately reflecting intravascular volume status or reliably correlating with the clinical manifestations of fluid accumulation is questionable (92-95).

The concept of "fluid overload" has been described in the literature using various definitions. Although some of the proposed definitions have been shown to correlate with outcomes, it is unclear how generalizable some of these findings are in light of study size and design limitations. The majority of prior studies were small, single center, and often evaluated fluid overload in specific clinical settings (such as bone marrow transplant or post–cardiac surgery patients). Significant discrepancy in fluid overload estimation can occur, depending on the definition used (96). Furthermore, none of these definitions integrated the rate of fluid accumulation and the time frame in which it occurred in relation to different phases of critical

illness. There is no broad consensus on how to precisely and reliably define the terms fluid accumulation and fluid overload, and we believe this may be hindering progress in the field.

In view of these limitations, we aim to conduct a systematic review and meta-analysis to appraise and synthesize the evidence describing the methods to measure fluid balance, define fluid overload, and evaluate the association between the various fluid-related metrics and outcomes in critically ill children. Synthesis of the available evidence is an important step in providing a foundation that will harmonize the various definitions of fluid metrics and help develop future interventional strategies to prevent or mitigate avoidable fluid accumulation and overload.

3.2 Objectives

- Describe the methods used to measure fluid balance in critically ill children
- Describe the definitions for fluid balance, fluid accumulation, and fluid overload in critically ill children
- Evaluate the association between fluid balance and mortality in critically ill children
- Evaluate the association between fluid balance and organ dysfunction and resource utilization in critically ill children

3.3 Methods

Study Design

We will perform a systematic review and meta-analysis focused on critically ill children exploring the methods used to assess fluid balance, define fluid overload, and evaluate the

association between fluid balance and outcomes. Our review will follow the format recommended by the Cochrane and Center for Reviews and Dissemination, and described according to the PRISMA-P guideline (97, 98).

Study Registration

This systematic review has been registered with PROSPERO (CRD42016036209) on March 2016.

3.4 Criteria for Considering Studies for This Review:

Inclusion criteria

All included studies will fulfill each of these criteria:

1. Population: studies enrolling patients below 25 years of age, admitted to a pediatric critical care setting.
2. Design: studies reporting original data incorporating interventional (randomized controlled trials or quasi-randomized controlled trials), cohort or case-control studies.
3. Exposure: studies describe a measure of fluid balance, fluid accumulation, and/or fluid overload.
4. Outcome: studies describe at least one of the following outcomes of interest:

Primary outcome:

28-day mortality

Secondary outcomes:

- Severity of illness scores (eg, Pediatric Risk of Mortality [PRISM])
- Organ failure scores (eg, Pediatric Logistic Organ Dysfunction [PELOD])

- Specific organ system dysfunction:
- PaO2/FiO2 ratio and/or oxygenation index
- Receipt and duration of mechanical ventilation
- Receipt and duration of renal replacement therapy
- Receipt and duration of extracorporeal life support (ECLS)
- Duration of pediatric intensive care unit (PICU) and hospital length of stay

Exclusion criteria

1. Adult studies (age ≥25 years)
2. Neonatal studies inclusive of premature infants or infants younger than 4 weeks of age
3. Case reports, case series, or observational studies that do not include a control/comparator
4. Studies conducted in noncritical care settings

3.5 Search Strategy for Identification of Studies

The search strategy was developed in consultation with an experienced research librarian and independently peer-reviewed by a second librarian (99). The search will be inclusive of all publications from database inception to present. We will search Ovid MEDLINE In-Process & Other Non-indexed Citations and Ovid MEDLINE, Ovid EMBASE, Cochrane Library via Wiley, and ProQuest Dissertations and Theses Global. In addition, www.clinicaltrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) will be searched for ongoing and completed clinical trials. We will perform a search of selected conference proceedings held within the last 3 years for the Society of Critical Care Medicine (SCCM), Canadian Critical Care Society, the European Society of Intensive Care Medicine (ESICM), the International Symposium on Intensive Care and Emergency Medicine (ISICEM),

the World Federation of Pediatric Intensive and Critical Care Societies, American Society of Nephrology (ASN), International Society of Nephrology (ISN), International Symposium on AKI in Children, and International Conference on Paediatric Continuous Renal Replacement Therapy (pCRRT). There will be no language restriction. Authors will be contacted by email to request additional data not described in a primary publication or data from unpublished studies if applicable. Our search strategy will use a combination of subject headings and text words for concepts related to children, critical illness, and fluid balance (Appendix). Finally, we will manually search for relevant studies using reference lists of retrieved citations and prior reviews of similar topics. Search results will be organized using EndNote X7 citation management software (Thomson Reuters, Philadelphia, Pennsylvania).

3.6 Data Extraction and Analysis

All identified titles and abstracts of studies examining the association between fluid balance and outcomes in pediatric population will be initially assessed independently by 2 reviewers for potential relevance. Selected studies will be retrieved and then be subjected to a second phase of screening for eligibility, as determined by the eligibility criteria listed above. Reason(s) for ineligibility will be documented for all studies excluded in the second phase of screening. Disagreements will be resolved through discussion or by a third reviewer if necessary.

A standardized data extraction form (Appendix) will be piloted and then used to extract data from the reports of all included studies in duplicate, and independently by 2 reviewers. Discrepancies in extracted data will be resolved by consensus, and if consensus cannot be reached, decisions will be left to the senior author (S.M.B).

Abstracted data from each study will include the details on the following:

- Study design, methodology, analysis, funding source, registration, and publication details.
- Aggregate participant demographic characteristics (eg, age, sex, and race).
- Aggregate participant clinical characteristics (eg, comorbid diseases, admission diagnostic category, and surgical status).
- Operational definitions for fluid balance, accumulation, and fluid overload, data on daily and cumulative fluid balance, and proportion and timing of occurrence of fluid accumulation and fluid overload.
- All primary and secondary outcomes reported, with their effect size and confidence intervals.
- Study quality features (see below).

3.7 Assessment of Methodological Quality and Risk of Bias

Studies selected for retrieval will be assessed by 2 independent reviewers for methodological quality and risk of bias. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (S.M.B.). The Newcastle-Ottawa Scale (NOS) will be used to assess the methodological quality of the included study.

3.8 Data Synthesis/Analysis Plan

The results of our search will be reported in a PRISMA flowchart. We will present tables outlining (1) study characteristics, (2) risk of bias for each study, and (3) study results and their effect measures. Quantitative studies will, where possible, be pooled in statistical meta-analysis.

We will use random effects model to pool effect sizes for each outcome; study weights will be measured using the inverse variance method. Dichotomous outcomes will be reported, where possible, as pooled odd ratios and 95% confidence intervals based on the random effects model. Continuous outcomes will be reported using calculated weighted mean differences with their 95% confidence intervals. We will use the DerSimonian and Laird method to compute between-studies variance (100). Results will be presented in forest plot using Review Manager (RevMan 5.3) software. We will contact authors for missing data, and if not possible, the potential impact of missing data on the results will be reported in the "Discussion" section. If statistical pooling is not possible, or if there are data from only 1 study for an outcome, the findings will be presented in narrative form. A priori, we have not defined a degree of heterogeneity that would preclude meta-analytic pooling.

3.9 Assessment of Heterogeneity

Clinical heterogeneity will be assessed by comparing the populations, exposures, and outcome measurements in all included studies. We will address clinical heterogeneity using subgroup and sensitivity analyses. Heterogeneity will be assessed statistically using I2 statistics and categorized as <25%, 25% to 50%, 50% to 75%, and >75% (101). Heterogeneity will also be evaluated using forest plots and sensitivity analyses based on the different study designs included in the review.

3.10 Assessment of Reporting Bias

We will assess potential reporting bias using a funnel plot if a sufficient number of studies are identified (>10 studies). Visual assessment and variance-stabilizing regression method will be used to test funnel plot asymmetry.

3.11 Subgroup Analysis

Depending on the number of studies included in the final analysis, the following subgroup analyses will be performed:

1. Infants (<1 year of age) and older children.
2. Children with primary cardiac and noncardiac diagnosis.
3. Sepsis and nonsepsis diagnosis.
4. Surgical and nonsurgical admissions.

3.12 Discussion

While timely fluid administration can be lifesaving, it has been suggested that the accumulation of fluid after initial resuscitation and hemodynamic stabilization can contribute to potentially avoidable adverse consequences and less favorable outcomes. Available studies of fluid balance in pediatric critical illness show that positive fluid balance potentially exerts an independent increased risk for mortality and adverse events, including worsening pulmonary and kidney function, longer duration of mechanical ventilation, and longer duration of PICU stay. While provocative, current evidence is largely derived from small, single-center, retrospective cohort studies, where variable definitions for fluid overload have been applied. The prevention or attenuation of fluid accumulation could improve patient-centered outcomes and health resource utilization.

3.13 Expected Limitations

The review may be limited by the quality of the included studies and a lack of pediatric interventional studies focused on this subject. Differences in definitions of fluid balance and fluid overload between studies may restrict the ability to synthesize the study findings. It also may be limited because of significant clinical or statistical heterogeneity between studies. The absence of specific fluid metrics data in some studies may limit our ability to include them in the meta-analysis. The number of studies included in the final analysis, their sample size, and access to individual data will determine the ability to conduct the proposed subgroup analyses.

3.14 Conclusion

We will perform a systematic review and evidence synthesis of fluid balance, accumulation, and overload among critically ill children and its association with patient-centered and health services outcomes. We expect our review will describe the broad impact of fluid accumulation and provide a foundation that will harmonize the various definitions for fluid metrics. This will help the development of future interventional strategies to prevent or mitigate avoidable fluid accumulation with the goal of improving outcomes for critically ill children at high risk of adverse events.

3.15 Appendix

Appendix 3.1: MEDLINE search strategy.

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. Acute Kidney Injury/ 2. Acute Lung Injury/ 3. exp Cardiac Surgical Procedures/ 4. exp Critical Care/ 5. Critical Illness/ 6. Heart Defects, Congenital/su 7. exp Intensive Care Units/ 8. Kidney/in 9. Multiple Organ Failure/ 10. Multiple Trauma/ 11. exp Organ Transplantation/ 12. Postoperative Complications/ 13. exp Renal Replacement Therapy/ 14. Respiration, Artificial/ 15. Respiratory Insufficiency/ 16. exp Sepsis/ 17. Transplant Recipients/ 18. Transplantation/ 19. Transplants/ 20. (acute kidney adj (failure or injur* or insufficien*)).tw,kf. 21. acute lung injur*.tw,kf. 22. (acute renal adj (failure or injur* or insufficien*)).tw,kf. 23. (AKI or ALI).tw,kf. 24. ((artificial* or mechanic*) adj (respirat* or ventilat*)).tw,kf. 25. ((cardiac or heart) adj surg*).tw,kf. 26. (coronary care adj (department* or unit* or ward or wards)).tw,kf. 27. critical care.tw,kf,jw. 28. (critical* adj2 (department* or unit* or ward or wards)).tw,kf. 29. critical* ill*.tw,kf. 30. CRRT.tw,kf. 31. CVVH.tw,kf. 32. (haemo filtrat* or haemofiltrat* or hemo filtrat* or hemofiltrat*).tw,kf. 33. intensive care*.tw,kf,jw. 34. (intensive adj2 (department* or unit* or ward or wards)).tw,kf. 35. intensivist*.tw,kf. 36. (ICU* or NICU* or PICU* or SICU*).tw,kf. 37. (multi* organ adj (disfunction* or dis function* or dysfunction* or dys function* or failure*)).tw,kf. 38. (multi* system adj (disfunction* or dis function* or dysfunction* or dys function* or failure*)).tw,kf. 39. (polytrauma* or trauma*).tw,kf. 40. (post op* or postop*).tw,kf. 41. (renal replacement adj2 (therap* or treatm* or support*)).tw,kf.	42. (respiratory care adj (department* or unit* or ward or wards)).tw,kf. 43. respiratory failure.tw,kf. 44. RRT.tw,kf. 45. (sepsis or septic*).tw,kf. 46. transplant*.tw,kf. 47. or/1-46 48. Body Fluids/ 49. Diuretics/ 50. Fluid Therapy/ 51. exp Solutions/ad, ae 52. Water-Electrolyte Imbalance/ 53. Water Intoxication/ 54. diuretic*.tw,kf. 55. (fluid* adj1 (accumulat* or administ* or balance or excess* or imbalance or manag* or over load* or overload* or retain* or retention or remov*)).tw,kf. 56. or/48-55 57. exp Adolescent/ 58. exp Child/ 59. exp Infant/ 60. exp Infant, Newborn Diseases/ 61. exp Infant, Premature, Diseases/ 62. exp Minors/ 63. Neonatology/ 64. exp Pediatrics/ 65. Perinatal Care/ 66. Perinatology/ 67. Postnatal Care/ 68. Premature Birth/ 69. exp Puberty/ 70. (baby* or babies or infant* or infancy or new born* or newborn*).tw,kf. 71. (boy* or girl* or teen*).tw,kf. 72. (child* or kid or kids or pre school* or preschool* or school age* or schoolchild* or toddler*).tw,kf. 73. (ELBW* or VLBW*).tw,kf. 74. low birth weight.tw,kf. 75. minors*.tw,kf. 76. (neonat* or perinat* or postnat*).tw,kf. 77. (paediatric* or peadiatric* or pediatric*).tw,kf,jw. 78. (prepubescen* or pubescen* or pubert*).tw,kf. 79. small for gestational age.tw,kf. 80. or/57-79 81. and/47,56,80 82. animals/ not (animals/ and humans/) 83. 81 not 82 84. (case reports or comment or editorial or letter).pt. 85. 83 not 84 86. remove duplicates from 85

Appendix 3.2: Data extraction form

Study identification	
Study ID	
Title	
Authors	
Country	
Citation (Journal, year, Vol, page)	
Study funding source	
Study registration #	
Study eligibility	
Age: 0-<25 yrs	☐Yes ☐ No
Study type	
Study settings	☐PICU ☐NICU ☐Non-PICU
Outcome(s) reported (at least one)	☐Mortality ☐Mechanical ventilation ☐Oxygenation index or PaO2/FiO2 ☐Organ system dysfunction scores ☐AKI ☐CRRT ☐ECMO/VAD ☐PICU LOS ☐Hospital LOS
☐ INCLUDED ☐ EXCLUDED	
Reason(s) for exclusion	
Population and settings	
Settings/Population (PICU type)	
Study inclusion criteria	

Study Exclusion criteria		
Methods		
Aim of study (as stated in paper)		
Study duration		
Start-end date		
Ethics approval	☐Yes ☐No ☐Not needed	
Risk of bias assessment (N-O scale) scores		
Selection	Comparability	Outcome
Participants		
Total no. included		
Age		
Sex		
Other reported sociodemographics		
Admission diagnoses		
Other co-morbidities		
Severity of illness scores		
Organ failure scores		
Intervention/exposure		
Intervention/Exposure included		
Fluid balance calculation method		
Definition of FO (if any)		
Other reported fluid measurements		

Outcomes:		
	Exposure	Control
n=		
FO		
Other fluid measurements		
Mortality at 28 days		
Mechanical ventilation		
Duration of mechanical ventilation		
Oxygenation Index		
PaO_2/FiO_2 ratio		
AKI		
CRRT		
ECMO		
PICU LOS		
Hospital LOS		
Other reported results		

CHAPTER 4

Association Between Fluid Balance and Outcomes in Critically Ill Children: A Systematic Review and Meta-Analysis

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ABSTRACT

Importance:

After initial resuscitation, critically ill children may accumulate fluid and develop fluid overload. Accruing evidence suggests that fluid overload contributes to greater complexity of care and worse outcomes.

Objective:

To describe the methods to measure fluid balance, define fluid overload, and evaluate the association between fluid balance and outcomes in critically ill children.

Data Sources:

Systematic search of MEDLINE, EMBASE, Cochrane Library, trial registries, and selected gray literature from inception to March 2017.

Study Selection:

Studies of children admitted to pediatric intensive care units that described fluid balance or fluid overload and reported outcomes of interest were included. No language restrictions were applied.

Data Extraction and Synthesis:

All stages were conducted independently by 2 reviewers. Data extracted included study characteristics, population, fluid metrics, and outcomes. Risk of bias was assessed using the Newcastle-Ottawa Scale. Narrative description of fluid assessment methods and fluid overload definitions was done. When feasible, pooled analyses were performed using random-effects models.

Main Outcomes and Measures:

Mortality was the primary outcome. Secondary outcomes included treatment intensity, organ failure, and resource use.

Results:

A total of 44 studies (7507 children) were included in this systematic review and meta-analysis. Of those, 27 (61%) were retrospective cohort studies, 13 (30%) were prospective cohort studies, 3 (7%) were case-control studies, and 1 study (2%) was a secondary analysis of a randomized trial. The proportion of children with fluid overload varied by case mix and fluid overload definition (median, 33%; range, 10%-83%). Fluid overload, however defined, was associated with increased in-hospital mortality (17 studies [n = 2853]; odds ratio [OR], 4.34 [95% CI, 3.01-6.26]; I2 = 61%). Survivors had lower percentage fluid overload than nonsurvivors (22 studies [n = 2848]; mean difference, −5.62 [95% CI, −7.28 to −3.97]; I2 = 76%). After adjustment for illness severity, there was a 6% increase in odds of mortality for every 1% in- crease in percentage fluid overload (11 studies [n = 3200]; adjusted OR, 1.06 [95% CI, 1.03-1.10]; I2 = 66%). Fluid overload was associated with increased risk for prolonged mechanical ventilation (>48 hours) (3 studies [n = 631]; OR, 2.14 [95% CI, 1.25-3.66]; I2 = 0%) and acute kidney injury (7 studies [n = 1833]; OR, 2.36 [95% CI, 1.27-4.38]; I2 = 78%).

Conclusion and Relevance:

Fluid overload is common and is associated with substantial morbidity and mortality in critically ill children. Additional research should now ideally focus on interventions aimed to mitigate the potential for harm associated with fluid overload.

KEY POINTS

Question

Is there an association between fluid balance and outcomes in critically ill children admitted to pediatric intensive care?

Findings

This systematic review and meta-analysis showed strong and consistent evidence of association between fluid overload and poor outcomes in critically ill children including: worsening respiratory function, development of acute kidney injury, longer pediatric intensive care stay and death.

Meaning

Fluid overload appears to be an important modifier of outcome in critically ill children, implying additional research is needed focused on strategies for preventing and/or mitigating this risk.

4.1 Introduction:

Fluid therapy is the cornerstone of resuscitation in critically ill children. Reestablishment of adequate intravascular volume using early aggressive fluid administration can be lifesaving (102, 103). However, beyond fluid therapy directed at resuscitation, critically ill children often receive variable amounts of "obligatory" fluid intake as part of their management (i.e., nutrition, medications, maintenance fluid). This cumulative fluid delivery frequently exceeds fluid loss, leading to a net positive fluid balance. A growing body of circumstantial evidence suggests that fluid accumulation after initial resuscitation may exert hazard for major morbidity and mortality (88, 90, 91, 104). These observations highlight the importance of monitoring fluid status and daily evaluation of critically ill children for avoidable fluid accumulation.

The concept of "fluid overload" has been described in the literature using various definitions (96, 105-107). Although some of the proposed definitions have shown strong correlation with outcomes, it is unclear how generalizable these findings are considering limitations in study design, size and methodology, and variation in case-mix. There are concerns about potential discrepancy in fluid overload estimation contingent on the definition applied (96). Moreover, there is no clear consensus on how to precisely and reliably define fluid overload.

Our aim was to describe the methods used to assess fluid balance, describe the definitions for fluid overload and evaluate the association between fluid balance and outcomes in critically ill children. We contend a rigorous synthesis of available evidence is needed to harmonize the

definitions of fluid metrics and aid in the development of management strategies to prevent or mitigate avoidable fluid overload.

4.2 Methods:

This review followed an *a priori* protocol that was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42016036209) and previously published. We followed the formats recommended by the Cochrane Center for Reviews and Dissemination, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (97, 98).

4.2.1 Data Sources and Searches:

The search strategy was developed and executed in consultation with an experienced research librarian and independently peer-reviewed by a second librarian. We executed our original search in June 2016 and completed an updated search in March 2017. No language or publication date restrictions were applied (Appendix 3.1).

We searched Ovid Medline (1946-), Ovid EMBASE (1974-), Cochrane Library via Wiley (inception-), and ProQuest Dissertations and Theses Global (1861-). Additionally, ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) were searched for ongoing and completed clinical trials. Proceedings of selected relevant pediatric, critical care and nephrology conferences in the last 3 years were manually searched (eTable 4.1). A manual search using reference lists of retrieved citations was conducted for other relevant studies.

4.2.2 Study Selection:

Potentially relevant citations were identified through independent screening of search result titles and abstracts by two of the authors (R.A. and E.S.). The selected studies were then retrieved and subjected to a second screening phase for eligibility using standard, pre-defined eligibility criteria. Disagreements were resolved through discussion with input from the senior author (S.M.B). Eligible studies had the following criteria: (1) population that was limited to patients under 25 years of age who were admitted to a pediatric ICU setting; (2) original data from interventional (randomized controlled trials or quasi-randomized controlled trials), cohort, or case-control studies; (3) description of a measure of fluid balance, fluid accumulation, and/or fluid overload; and (4) contained at least one outcome of interest. Studies were excluded if they had one of the following characteristics: (1) inclusion of patients ≥25 years of age; (2) primary neonatal studies inclusive of premature infants or infants less than 4 weeks of age; (3) case reports, case series, review papers, or observational studies without a control/comparator; or (4) studies conducted in a non-critical care setting.

4.2.3 Outcome Measures:

The primary outcome was all-cause mortality, as defined by included studies. Secondary outcomes included respiratory outcomes, acute kidney injury (AKI), pediatric intensive care (PICU) length of stay, and other reported measures of treatment intensity, organ failure and health resource utilization.

4.2.4 Data Extraction:

A structured data extraction form was piloted and then used to extract data from the reports of all included studies in duplicate, and independently by two reviewers (R.A. and E.S.). Discrepancies in extracted data was resolved through discussion. Both crude and adjusted statistics were collected. Where relevant, attempts were made to contact authors for missing data.

4.2.5 Quality Assessment:

Two authors (R.A. and E.S.) independently assessed the risk of bias using the Newcastle-Ottawa scale (108), and any discordant assessments were resolved via discussion. We considered a study of good quality if its total score was at least 8, fair quality if the score was 5-7, and poor quality if the score was 4 or lower.

4.2.6 Data Synthesis and Analysis:

The included studies were arranged based on exposure (i.e., the main measure used to describe fluid balance) and outcomes of interest. Within each group, studies were further clustered based on whether the exposure was dichotomous or continuous. For dichotomous outcomes, odds ratios (OR) were used as the common measure of association with their 95% confidence intervals (CI). Continuous outcomes were reported as weighted mean differences (WMD) with their 95% CI. Where necessary, means and standard deviations were estimated from median and interquartile range using a standard approach (109). We used random-effects

models for pooled analyses because of anticipated heterogeneity. Statistical analyses were performed using Review Manager (RevMan [computer program]. Version 5.3. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014). When statistical pooling was not possible, due to exposure-outcome heterogeneity or insufficient number of studies for an outcome or exposure, the findings were described in narrative form.

4.2.7 Assessment of Heterogeneity and Reporting Bias:

Clinical heterogeneity was addressed by performing sub-group analyses based on populations, exposures and outcome measurements in all included studies. Statistical heterogeneity was evaluated using I^2 statistics, with estimate of 50% or higher considered as significant heterogeneity. Visual assessment of funnel plot was used to evaluate reporting bias in analyses with sufficient number of studies (>10 studies) (110).

4.3 Results:

The literature search identified 7211 potentially relevant studies. Forty-four studies, including 7507 patients, fulfilled all eligibility criteria (Figure 4.1). Of those, 27 (61%) were retrospective cohort, 13 (30%) were prospective cohort, 3 (6%) were case-control studies and one study was a secondary analysis of a randomized trial. Of the included studies: 15 (34%) were performed in cohorts of patients receiving renal replacement therapy (RRT), 9 (20%) in multi-system PICU, 6 (14%) in post-cardiac surgery, 5 (11%) in sepsis, 4 (9%) in stem cell transplant, and 2 (4%) in extracorporeal membrane oxygenation (ECMO) supported children (Table 4.1).

The median risk of bias score was 8 (range, 6-9). Fourteen studies (32%) were labeled as fair quality, while the remaining 30 studies (68%) were of good quality. The main potential sources of bias were "representativeness of the cohort" and "comparability" which required the adjustment for the confounders age and severity of illness in the analysis (eTable 4.2).

4.3.1 Fluid Balance Assessment:

Four different fluid metrics were used to describe fluid balance: cumulative or peak percent fluid overload (%FO) (37 studies), cumulative or peak percent weight change (4 studies), net fluid balance in relation to weight (5 studies), and net fluid balance in relation to body surface area (1 study) (eTable 4.3).

Percent fluid overload was calculated using the following formula: [(total fluid intake (Liter) – total fluid output (Liter) /admission weight (Kilogram)] x 100. This equation was based on the literature: (59-62, 85-87, 90, 91, 96, 104-107, 111-131)

Percent weight change was calculated as follow: [(current weight – admission weight)/admission weight] x 100. This equation was taken from relevant studies: (96, 106, 107, 132)

PICU admission weight was used as the denominator "admission weight" in 22 studies, hospital admission weight (7 studies), out-patient weight (2 studies), dry or ideal body weight (2 studies) and in 13 studies the weight used was not specified (eTable 4.4).

Three studies compared the fluid intake-output and weight-based methods. In a small cohort of stem cell transplant patients, Lombel et al (96) described significant variability in fluid balance calculations, with the fluid intake-output method showing greatest correlation and effect on outcomes in adjusted analysis. The weight-based method was significantly associated with outcomes only when PICU admission weight was used instead of hospital admission weight or estimated dry weight. Hazle et al (107) reported significant correlation between the two methods ($r = 0.65$, $p < 0.0001$) in post-cardiac surgery infants, although percent fluid overload was an independent predictor of poor outcome in adjusted analysis only when calculated by the weight-based method. Alternatively, in a cohort of patients receiving CRRT, Selewski et al (106) reported significant correlation and comparable predictive values between these two methods.

4.3.2 Fluid Overload Definitions

Twenty-six studies identified specific threshold values to define fluid overload: >5% (n=4), >7% (n=1), >10% (n=15), >13% (n=1), >15% (n=1), and >20% (n=10). The assessment period varied from 24-hours post PICU admission to the entire PICU stay (Table 4.2). Depending on the population and fluid overload definition used, the proportion of patients identified as having fluid overload (dichotomous exposure) ranged between 10% (in post-cardiac surgery) to 83% (in ECMO patients receiving RRT), with a pooled median of 32.7%. Three studies described the time to maximum percent fluid overload (continuous exposure). Arikan et al, reported that maximum %FO was achieved on day 5.7 ± 4.2 in a cohort of general PICU patients receiving mechanical ventilation (86). In two studies of post-cardiac surgery patients, %FO peaked within the first 24-48 after surgery (129, 130).

4.3.3 Outcomes:

Mortality

Seventeen studies evaluated mortality utilizing fluid overload as a dichotomous exposure. Fluid overload, however defined across studies, was associated with increased in-hospital mortality (OR, 4.34 [95%CI, 3.01-6.26]; I^2=61%, n=2835) (Figure 4.2). This association between fluid overload and mortality was robust in sensitivity analysis that included data from only 6 studies that adjusted for illness severity (adjusted-OR, 4.38 [95%CI, 2.64-7.28]; I^2=14%, n=782) (eFigure 4.1). Similarly, sensitivity analysis that included non-RRT studies only showed significant association with mortality (OR, 6.20 [95% CI, 2.89-13.28]; I^2=80%, n= 1868) (eFigure 4.2).

We pooled studies that used similar fluid overload threshold and duration of assessment. This resulted in 4 different fluid overload definitions, all of which showed significant association with mortality and low statistical heterogeneity (Figure 4.3):

- Definition 1: Cumulative percent fluid overload >5% during the first 24 hours of admission (OR, 9.35 [95% CI, 5.05- 17.29]; I^2=0%, n=572)
- Definition 2: Peak percent fluid overload >10% at any point during entire PICU admission (OR, 15.02 [95%CI, 7.09-31.82]; I^2=0%, n=322)
- Definition 3: Cumulative percent fluid overload >10% at CRRT initiation (OR, 2.82 [95% CI, 1.95-4.10]; I^2=0%, n=451)
- Definition 4: Cumulative percent fluid overload >20% at CRRT initiation (OR, 4.29 [95% CI, 2.78-6.62]; I^2=0%, n=460)

When fluid overload was evaluated as a continuous exposure (22 studies), survivors had lower percent fluid overload compared to non-survivors (WMD, -5.62; [95%CI, -7.28, -3.9], I^2=76%, n=2848) (Figure 4.4). There was marked variation in the periods during which percent fluid overload was assessed (eFigure 4.3). Among 11 studies that adjusted for illness severity, pooled analysis found 6% increased odds of mortality for every 1% increase in fluid overload (adjusted-OR 1.06; [95%CI, 1.03-1.10]; I^2=66%, n=3200) (eFigure 4.4). Funnel plots of fluid overload percentage (as a categorical and continuous variable) association with mortality are shown in eFigure 4.8 and eFigure 4.9 in the appendix.

Respiratory Outcomes

Respiratory dysfunction and outcomes, including change in oxygenation index, ventilation-free days or length of mechanical ventilation, were evaluated in 19 studies. Of these, 15 studies (79%) reported that positive fluid balance or fluid overload were associated with negative outcomes (eTable 4.5). Six studies reported significant correlation between increasing fluid overload and worsening oxygenation index (85, 86, 126, 129, 130, 133). In addition, 3 studies showed that greater percent fluid overload was an independent predictor of worsened oxygenation index (85, 86, 130). In 3 studies of children with acute lung injury, positive fluid balance was associated with fewer ventilation-free days (88, 89, 133). Pooled data from 3 studies demonstrated that fluid overload was associated with prolonged mechanical ventilation (>48hrs) (OR 2.14; [95%CI, 1.25-3.66], I^2=0%, n=631) (eFigure 4.5). Pooled analyses of the remaining data were not feasible due to marked clinical and statistically heterogeneity in exposure-outcome combinations.

Acute Kidney Injury

Data from 7 studies demonstrated that fluid overload was associated with increased risk of AKI (OR 2.36; [95%CI, 1.27- 4.38], I^2=78%, n=1833) compared to those without fluid overload (eFigure 4.6). In one study, fluid overload was significantly associated with longer time to kidney recovery in a cohort of children receiving CRRT (87).

PICU Length of Stay

Pooled data from 6 studies showed that fluid overload was associated with longer PICU stay compared to no fluid overload (WMD -2.51 [95%CI, -4.99, -0.03], I^2=88%, n=1001] (eFigure 4.7). Three additional studies reported significant association between fluid overload and increased PICU length of stay; however, data could not be pooled statistically (86, 116, 129).

Additional outcomes, including utilization of RRT, ECMO and composite outcomes associated with fluid overload are described in eTable 4.6.

4.4 Discussion:

In this rigorous and comprehensive systematic review, we synthesized the evidence from 44 studies including 7507 children to describe the methods used to assess fluid balance, define fluid overload and describe the association between fluid balance and outcomes in critically ill children. We found the current evidence to be largely comprised of small observational studies applying heterogeneous metrics to assess fluid balance and define fluid overload. This variation was particularly evident in 3 areas: 1) the methods used to measure fluid balance; 2) the methods used to quantify fluid overload; 3) the thresholds and duration of fluid overload assessment in relation to outcome assessment. Nevertheless, our findings were robust

and consistent in suggesting that fluid overload was common and portended greater risk for death, worsened respiratory physiology including prolonged mechanical ventilation, and additional outcomes implying greater intensification of support. These findings align with growing evidence describing the negative association between fluid accumulation and outcomes in adult critically ill populations including acute respiratory distress syndrome (134-136), sepsis (137-139), AKI (49, 50, 140, 141) and in perioperative settings (142-145).

Despite accumulating observational data showing the harmful impact of fluid overload on outcomes, there is currently no consensus on how best to define it. The current definitions of fluid overload include three components:

1) Methods of fluid balance assessment: Accurate monitoring of fluid balance is an imperative first step to recognize fluid overload. We identified two main methods of assessing fluid balance based either on recorded daily intake-output or serial weight measurements. Recording daily intake and output can be time consuming to track and prone to error. Serial weight measurements offer some theoretical advantages including presumed integration of insensible fluid losses. However, frequent weight measurements might not be feasible in the PICU environment due to the unstable condition of many PICU patients. More objective tools such as electrical bioimpedence and point of care ultrasound have shown promise in providing more objective assessment of fluid status. However, none of the studies identified in this review evaluated their clinical utility.

2) Methods used to quantify fluid overload: The calculation of percent fluid overload proposed by Goldstein and colleagues (105) was the most frequently used method to quantify fluid overload. Some studies used percent weight change as an alternative. Two of the three studies

that compared both methods showed that they were highly correlated (106, 107). Based on that, and until further evidence suggests otherwise, it seems reasonable to consider both methods to be clinically useful.

3) Threshold and duration of fluid overload assessment: While various combinations of thresholds and durations were utilized, we identified 4 common definitions. All 4 definitions showed significant association with outcomes:

a) Early fluid overload: cumulative percent fluid overload >5% in the first 24 hours
b) Peak percent fluid overload >10% during PICU admission
c) Cumulative percent fluid overload >10% at CRRT initiation
d) Cumulative percent fluid overload >20% at CRRT initiation

These definitions align with similar threshold of 10% that have been used in some adult studies and showed association with worse outcomes (140, 141).

Available evidence describing the negative impact of fluid overload highlights the potential for evaluation of strategies to prevent, mitigate and manage fluid accumulation in critically ill children. Clinical trials have suggested conservative fluid management strategies are feasible and may be associated with improved outcomes. The Fluid and Catheter Treatment Trial (FACTT) reported that a conservative fluid management strategy during the first 7 days of ICU admission among adult with acute lung injury portended shorter duration of mechanical ventilation and ICU stay when compared to a liberal fluid management (135). However, in a planned secondary analysis, those allocated to the conservative strategy showed greater risk of cognitive impairment compared with those in the liberal management group, a finding that

demands consideration in the context of critically ill children (146). The FEAST study was a randomized controlled trial of 3141 African children with severe febrile illness and clinical evidence of organ hypoperfusion (147). Children were randomized to receive fluid boluses with 20-40 ml/kg (0.9% saline or 5% albumin) or no fluid bolus therapy. Children receiving fluid boluses had significantly greater mortality within 48 hours due largely to cardiovascular collapse (148). While FEAST has limited generalizability to modern PICU care, it certainly raises concerns about our primitive understanding of the context and volume of fluid administered to critically ill children both acutely and during their PICU course and its association with outcomes. Two pilot studies have shown that a restrictive fluid management strategy after initial resuscitation is safe in septic adults (149, 150). A similar study in children is currently underway: the SQUEEZE (septic shock reversal is quicker in pediatric patients randomized to an early goal directed fluid-sparing strategy vs. usual care) (151).

Our findings also suggest that fluid balance may represent an identifiable and modifiable target for intervention. The concept of "active de-resuscitation" after initial stabilization using pharmacological or extracorporeal interventions has been introduced in the literature (152). A post hoc analysis of the FACTT trial showed that diuretic-induced negative fluid balance was associated with improved survival in adults with AKI (49). In a recent RCT involving 73 post-cardiac surgery infants, prophylactic peritoneal dialysis was more effective than furosemide in mitigating the development of fluid overload (>10%) and associated with shorter duration of mechanical ventilation and inotrope use (81). However, it currently remains uncertain whether the earlier initiation of RRT in critical illness, particularly when confronted with AKI and fluid accumulation, can improve outcomes (63, 64). The data summarized in our review would appear

to support the evaluation of active strategies to prevent and mitigate fluid overload in critically ill children and should be tested in rigorous clinical trials.

Strengths and Limitations

Our systematic review is strengthened by employing a comprehensive search strategy, by rigorous screening and eligibility criteria, and by transparent reporting of our findings. We also found our primary and secondary outcome findings were robust in sensitivity analyses considering pre-specified case-mix subgroups, variable fluid overload definitions and after including only studies where illness severity adjustment was possible. However, the studies included in our systematic review have important limitations. First, nearly all studies were observational, mostly retrospective with many having limited capacity for adjustment, and therefore are at risk of selection bias and residual confounding. Second, as such, we cannot definitively confirm the causal link between fluid overload and adverse outcomes given the paucity of rigorous experimental trials evaluating fluid management strategies in critically ill children. Third, studies included had wide variation in case-mix and in operational definitions for fluid balance and fluid overload, and significant heterogeneity in outcomes which limited our capacity for pooled analyses in selected circumstances. Moreover, selected studies reported fluid overload as continuous exposure using median and range necessitating transformation of the data to mean and standard deviation using previously described formulas. This may have contributed to imprecise effect estimates. Some PICU sub-populations, such as trauma and burn patients were underrepresented in the included studies which could limit the generalizability of the findings. Few studies evaluated the temporal changes in fluid balance during PICU course. Finally, few studies considered the potential fluid deficit state of children or accounted for fluid

administration and accumulation prior to PICU admission. This may have contributed to misclassification of fluid overload, when considering many PICU patients receive fluid resuscitation in the emergency department, operating theatre or on general wards prior to transfer to PICU.

4.5 Conclusion:

Fluid overload is common among critically ill children and exerts a strong negative association with outcomes. The findings of our systematic review support the hypothesis that a threshold may exist beyond which fluid accumulation becomes unhelpful or frankly harmful. Clinicians should monitor fluid balance and consider the hazard associated with avoidable fluid accumulation and overload. We believe our work further provides a foundation for development of optimal strategies for fluid management among critically ill children, specifically in the form of rigorous clinical trials, aimed specifically at avoiding and mitigating iatrogenic or avoidable fluid overload.

Conflict of Interest Disclosures:

None reported.

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Role of the Funder/Sponsor:

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions:

Tara Landry, MLIS (Montreal General Hospital Medical Library, Montreal, Quebec, Canada), reviewed the search strategy and received a stipend for peer reviewing the search strategy from the Alberta Strategies for Patient-Oriented Research (SPOR) SUPPORT Unit Knowledge Translation Platform.

Table 4.1: Characteristics of included studies

Study, Year	Country	Study Type	N	Age Mean ± SD (years)	Population	Main Fluid Measure(s)	Main Outcome(s)
Abulebda 2014	United States	RC	317	non-survivors = 2 ± 3.8 Survivors = 3.5 ± 4.1	Sepsis	%FO	Mortality Composite of complicated course
Arikan 2012	United States	RC	80	4.8 ± 6.1	Multisystem (ventilated only)	%FO	Mortality OI LMV PICU LOS
Askenazi 2013	United States	PC	84	1.03 ± 2.1	CRRT	%FO	Mortality
Baird 2010	United States	RC	39	8.8 ± 5.7	CRRT	%FO	Mortality
Bhaskar 2015	United States	case-control	114	4.8 ± 2.8	Sepsis/Shock	%FO	Mortality LMV PICU LOS ECMO
Boschee 2014	Canada	RC	90	2.5 ± 5.1	CRRT	%FO	Mortality
Chen 2016	China	RC	202	0.7 ± 0.9	Sepsis	%FO	Mortality LMV PICU LOS AKI
Choi 2017	South Korea	RC	123	n/a	CRRT	%FO	Mortality
Diaz 2017	United States	PC	224	4.6 ± 6.8	Multisystem	%FO	Mortality LMV PICU LOS
de Galasso 2016	Italy	RC	131	7.3 ± 8.1	CRRT	Fluid balance (ml/m2) %FO	Mortality
Elbahlawan 2010	United States	RC	30	10.3 ± 4.5	CRRT in stem cell transplant	%FO	Mortality PaO2/FiO2 ratio
Flores 2008	United States	PC	51	12.8 ± 5.8	CRRT in stem cell transplant	%FO	Mortality
Flori 2011	United States	PC	313	7.1 ± 13.3	ALI	Fluid balance (ml/kg/day)	Mortality VFD
Foland 2004	United States	RC	113	8.8 ± 8.8	CRRT	%FO	Mortality
Gillespie 2004	United States	RC	77	5.1 ± 5.7	CRRT	%FO	Mortality

Goldstein 2001	United States	RC	21	8.8 ± 6.3	CRRT	%FO	Mortality
Goldstein 2005	United States	PC	116	8.5 ± 6.8	CRRT in MODS	%FO	Mortality
Gulla 2015	India	RC	27	9.8 ± 3.7	CRRT in sepsis	%FO	Mortality
Hassinger 2014	United States	PC	98	FO = 1.1 ± 1.5 No FO = 5.8 ± 8.4	Post cardiac surgery	Fluid balance (ml/kg) %FO	LMV PICU LOS inotropic support AKI
Hayes 2009	United States	RC	76	7.6 ± 3.15	CRRT	%FO	Mortality LMV PICU LOS Time to renal recovery
Hazle 2013	United States	PC	49	0.2 ± 0.2	Post cardiac surgery	%FO %weight change	Composite of poor outcome
Hoover 2008	United States	Case-control	52	ECMO with CRRT = 5.2 ± 4 ECMO without CRRT = 5.4 ± 4.3	CRRT in ECMO	Fluid balance (ml/kg/day)	Mortality
Inglese 2017	Netherlands	RC	135	1.8 ± 1.4	Ventilated PICU patients	Fluid balance (ml/kg)	LMV OI
Jhang 2014	Korea	RC	87	7.9 ± 6.4	CRRT	%FO	Mortality
Kaempfen 2017	United Kingdom	RC	71	Non-Survivors = 0.3 ± 0.5 survivors = 0.4 ± 0.6	CRRT	%FO	Mortality
Ketharanathan 2014	South Africa	PC	100	1.4 ± 2.9	Multisystem	%FO	Mortality LMV Oxygenation index
Lex 2016	Hungary	PC	1520	FO = 0.6 ± 0.8 No FO = 2.4 ± 3.8	Post cardiac surgery	Fluid balance (ml/kg) %FO	Mortality LMV Low cardiac output syndrome
Li 2016	China	PC	370	FO = 0.9 ± 1.3 No FO = 1.4 ± 2.1	Multisystem	%FO	Mortality LMV PICU LOS AKI
Lombel 2012	United States	RC	21	4.4 ± 1.5	CRRT post stem cell transplant	%FO %weight change	Mortality

Michael 2004	United States	RC	26	13 ± 5	Stem cell transplant	%FO	Mortality
Modem 2014	United States	Case-control	190	10.4 ± 3.7	CRRT	%FO	Mortality
Naveda 2016	Venezuela	PC	102	6.6 ± 3.3	Sepsis	Fluid balance (ml) %FO	Mortality
Park 2016	South Korea	RC	220	No AKI = 1.2 ± 1.8 AKI = 0.3 ± 0.3	post cardiac surgery	%FO	AKI
Randolph 2005	United States	PC	301	n/a	Multisystem (Ventilated only)	Fluid balance (ml/kg)	LMV Extubation failure
Sampaio 2015	Canada	RC	85	3.6 ± 3.1	Post cardiac surgery	%FO	LMV OI Extubation failure PICU LOS
Seguin 2014	Canada	RC	193	2.6 ± 4.2	Post cardiac surgery	%FO	LMV OI PICU LOS AKI
Selewski 2011	United States	RC	113	5.5 ± 11.2	CRRT	%FO %weigh change	mortality
Selewski 2012	United States	RC	53	0.3 ± 0.6	CRRT in ECMO	%weight change	Mortality
Sinitsky 2015	United Kingdom	RC	636	1.8 ± 2.8	Multisystem	%FO	Mortality LMV OI Need for RRT
Sutherland 2010	United States	PC	297	8.5 ± 7	CRRT	%FO	Mortality
Sutawan 2016	Indonesia	Case-control	120	non-survivors= 3.3 ± 1.9 survivors = 3.4	Multisystem	%FO	Mortality
Valentine 2012	United States	RC	168	4.9 ± 7.5	ALI	Fluid balance (ml/kg)	Mortality VFD
Vidal 2016	Argentina	RC	163	1.6 ± 2.1	Ventilated PICU patients	%FO	LMV
Willson 2013	United States	RCT	109	6.1 ± 5.8	ALI	Fluid balance (ml/m2)	Mortality OI VFD

Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; CC, case control; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FIO2, fraction of inspired oxygen; FO, fluid overload; %FO, percentage fluid overload; LMV, length of mechanical ventilation; LOS, length of stay; MODS, multiorgan dysfunction syndrome; NA, not available; OI oxygenation index; PaO2, partial pressure of oxygen in arterial blood; PC,prospective cohort; PICU, pediatric intensive care unit; RC, retrospective cohort; RCT, randomized clinical trial; RRT, renal replacement therapy; VFD, ventilation-free days.

Table 4.2: Fluid overload definitions

%FO cut off	Weight Used	Assessment Period		Study
		Start	End	
FO% >5%	Not specified	PICU admission	POD1	Hassinger, 2014
	PICU admission weight		24 hr post admission	Chen, 2016
				Li, 2016
	hospital admission weight or the most recent PICU weight	Intraoperative	POD 2	Lex, 2016
FO% >7%	Not specified	Intraoperative	POD 3	Park, 2016
FO% >10%	PICU admission weight	PICU admission	CRRT initiation	Askenazi, 2013 Boschee, 2014 de Galasso, 2016 Gillespie, 2004 Selewski, 2012 Sutherland, 2010
		Not specified		Modem, 2014
	Not specified	24 hr prior to CRRT		Elbahlawan, 2010
	Hospital admission weight	Hospital admission	Not specified	Michael, 2004
	PICU admission weight	PICU admission	PICU day 2	Sinitsky, 2015
			PICU day 3	Bhaskar,2015
		Not specified	Not specified	Sutawan, 2016
	Pre-operative weight	PICU admission	PICU day 7	Hazle, 2013
	PICU admission weight		PICU discharge	Ketharanathan, 2014
	Not specified			Nevada, 2016
FO% >13%	Not specified	PICU admission	PICU day 2	Vidal, 2016
FO% >15%	PICU admission weight	PICU admission	14 days	Arikan, 2012
FO% >20%	PICU admission weight	PICU admission	PICU discharge	Diaz, 2017
			CRRT initiation	Askenazi, 2013 Goldstein, 2005 Jhang, 2014 Selewski, 2012 Sutherland, 2010
		Not specified		Modem, 2014
	Hospital admission weight	PICU admission		Hayes, 2009
			PICU day 2	Sinitsky, 2015
	Pre-operative weight		PICU day 7	Hazle, 2013

Figure 4.1: Study Selection

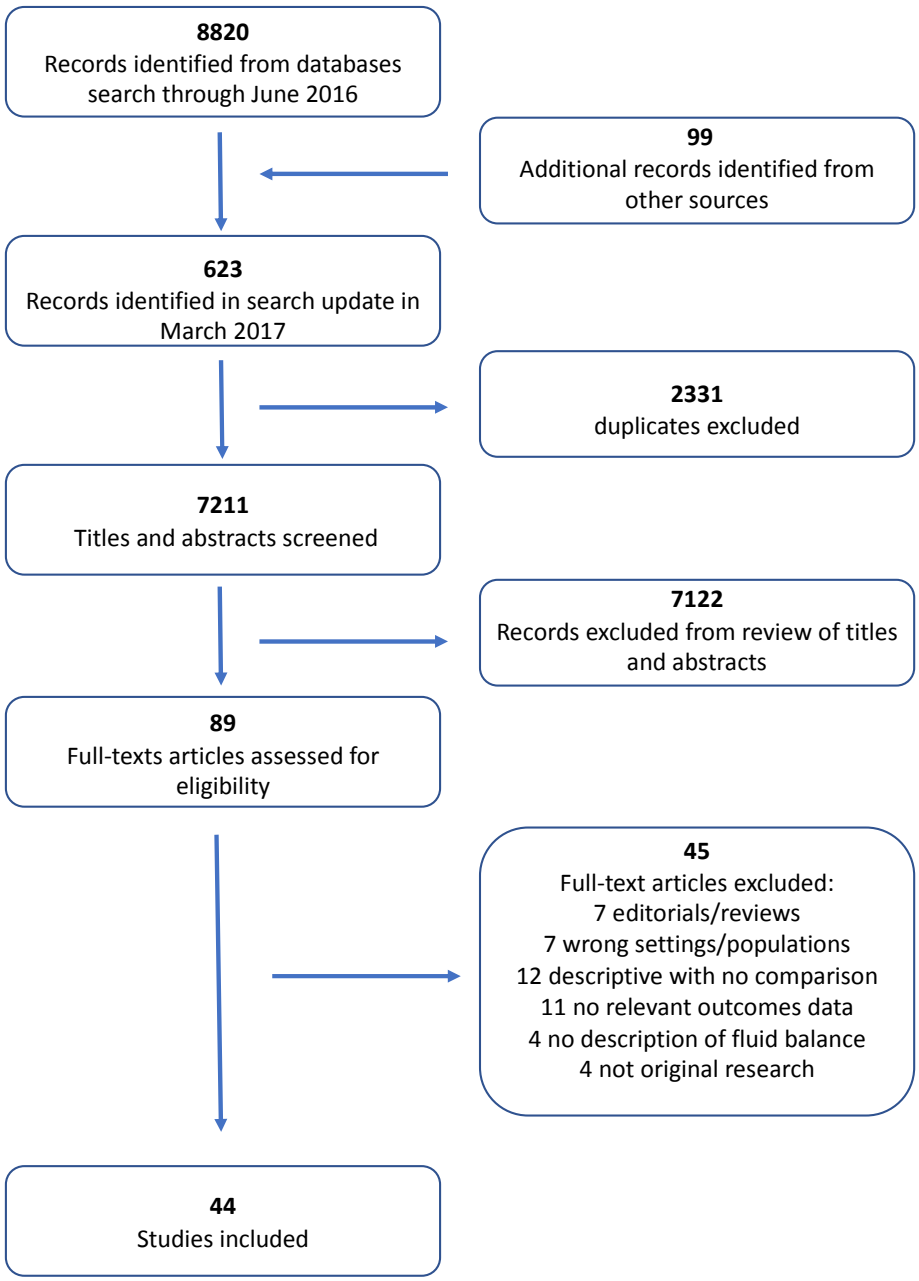


Figure 4.2:

Figure 1. Random-Effects Meta-analysis of Fluid Overload (Categorical Exposure) and Mortality Stratified by Case Mix

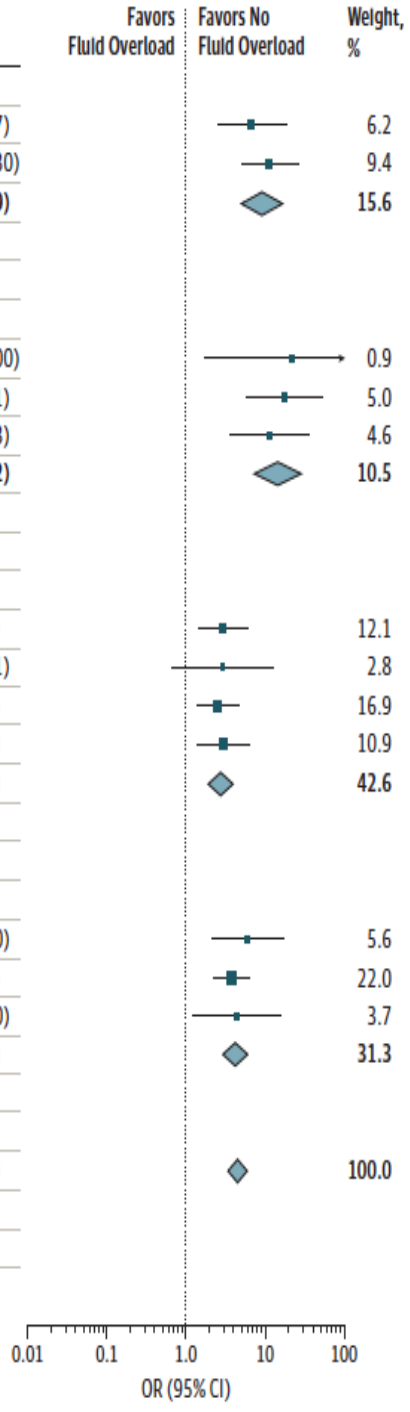
Source	Log (OR)	SE	OR (95% CI)	Weight, %
CRRT				
Gillespie et al,[31] 2004	1.1053	0.3570	3.02 (1.50-6.08)	7.9
Michael et al,[42] 2004	1.9459	0.8997	7.00 (1.20-40.82)	3.1
Hayes et al,[35] 2009	1.8036	0.5252	6.07 (2.17-17.00)	5.9
Elbahlawan et al,[28] 2010	-0.2719	1.2440	0.76 (0.07-8.73)	1.9
Sutherland et al,[51] 2010	1.3604	0.2643	3.90 (2.32-6.54)	9.0
Selewski et al,[49] 2012	1.0922	0.7478	2.98 (0.69-12.91)	4.0
Modem et al,[43] 2014	0.9442	0.3021	2.57 (1.42-4.65)	8.6
Jhang et al,[38] 2014	1.4956	0.6452	4.46 (1.26-15.80)	4.8
de Galasso et al,[27] 2016	1.0963	0.3765	2.99 (1.43-6.26)	7.6
Subtotal (95% CI)			**3.37 (2.55-4.44)**	**52.6**
Heterogeneity: $\tau^2=0.00$; $\chi^2_8=4.86$, ($P=.77$); $I^2=0\%$				
Test for overall effect: $z=8.57$, ($P<.001$)				
Sepsis/shock				
Bhaskar et al,[5] 2015	1.7971	0.6228	6.03 (1.78-20.45)	4.9
Chen et al,[24] 2016	2.4368	0.4052	11.44 (5.17-25.30)	7.3
Naveda et al,[44] 2016	2.8856	0.5574	17.91 (6.01-53.41)	5.6
Subtotal (95% CI)			**11.24 (6.37-19.85)**	**17.8**
Heterogeneity: $\tau^2=0.00$; $\chi^2_8=1.70$, ($P=.43$); $I^2=0\%$				
Test for overall effect: $z=8.34$, ($P<.001$)				
General				
Ketharanathan et al,[40] 2014	3.1023	1.2792	22.25 (1.81-273.00)	1.8
Sinitsky et al,[50] 2015	0.4152	0.2926	1.51 (0.85-2.69)	8.7
Li et al,[6] 2016	1.9313	0.4969	6.90 (2.60-18.27)	6.2
Sutawan et al,[52] 2016	2.4384	0.5790	11.45 (3.68-35.63)	5.3
Diaz et al,[26] 2017	0.6799	0.3777	1.97 (0.94-4.14)	7.6
Subtotal (95% CI)			**4.22 (1.73-10.30)**	**29.6**
Heterogeneity: $\tau^2=0.72$; $\chi^2_8=17.10$, ($P=.002$); $I^2=77\%$				
Test for overall effect: $z=3.17$, ($P=.002$)				
Total (95% CI)			**4.34 (3.01-6.26)**	**100.0**
Heterogeneity: $\tau^2=0.31$; $\chi^2_8=41.11$, ($P<.001$); $I^2=61\%$				
Test for overall effect: $z=7.88$, ($P<.001$)				
Test for subgroup differences: $\chi^2_8=13.95$, ($P<.001$); $I^2=85.7\%$				

Included were 17 studies.[5,6,24,26-28,31,35,38,40,42-44,49-52] CRRT indicates continuous renal replacement therapy; and OR, odds ratio.

Figure 4.3:

Figure 2. Random-Effects Meta-analysis of Fluid Overload (Categorical Exposure) and Mortality Stratified by Fluid Overload Definition

Source	Log (OR)	SE	OR (95% CI)
Definition 1 (%FO >5% in 24 h)			
Li et al,[6] 2016	1.9313	0.4969	6.90 (2.60-18.27)
Chen et al,[24] 2016	2.4368	0.4052	11.44 (15.17-25.30)
Subtotal (95% CI)			**9.35 (5.05-17.29)**
Heterogeneity: $\chi^2_8 = 0.62$, ($P = .43$); $I^2 = 0\%$			
Test for overall effect: $z = 7.12$, ($P < .001$)			
Definition 2 (%FO >10% during PICU admission)			
Ketharanathan et al,[40] 2014	3.1023	1.2792	22.25 (1.81-273.00)
Naveda et al,[44] 2016	2.8856	0.5574	17.91 (6.01-53.41)
Sutawan et al,[52] 2016	2.4384	0.5790	11.45 (3.68-35.63)
Subtotal (95% CI)			**15.02 (7.09-31.82)**
Heterogeneity: $\chi^2_8 = 0.41$, ($P = .81$); $I^2 = 0\%$			
Test for overall effect: $z = 7.07$, ($P < .001$)			
Definition 3 (%FO >10% at CRRT Initiation)			
Gillespie et al,[31] 2004	1.1053	0.3570	3.02 (1.50-6.08)
Selewski et al,[49] 2012	1.0922	0.7478	2.98 (0.69-12.91)
Modem et al,[43] 2014	0.9442	0.3021	2.57 (1.42-4.65)
de Galasso et al,[27] 2016	1.0963	0.3765	2.99 (1.43-6.26)
Subtotal (95% CI)			**2.83 (1.95-4.10)**
Heterogeneity: $\chi^2_8 = 0.16$, ($P = .98$); $I^2 = 0\%$			
Test for overall effect: $z = 5.46$, ($P < .001$)			
Definition 4 (%FO >20% at CRRT Initiation)			
Hayes et al,[35] 2009	1.8036	0.5252	6.07 (2.17-17.00)
Sutherland et al,[51] 2010	1.3604	0.2643	3.90 (2.32-6.54)
Jhang et al,[38] 2014	1.4956	0.6452	4.46 (1.26-15.80)
Subtotal (95% CI)			**4.29 (2.78-6.62)**
Heterogeneity: $\chi^2_8 = 0.57$, ($P = .75$); $I^2 = 0\%$			
Test for overall effect: $z = 6.56$, ($P < .001$)			
Total (95% CI)			**4.62 (3.63-5.90)**
Heterogeneity: $\chi^2_8 = 23.08$, ($P = .02$); $I^2 = 52\%$			
Test for overall effect: $z = 12.34$, ($P < .001$)			
Test for subgroup differences: $\chi^2_8 = 21.31$, ($P < .001$); $I^2 = 85.9\%$			

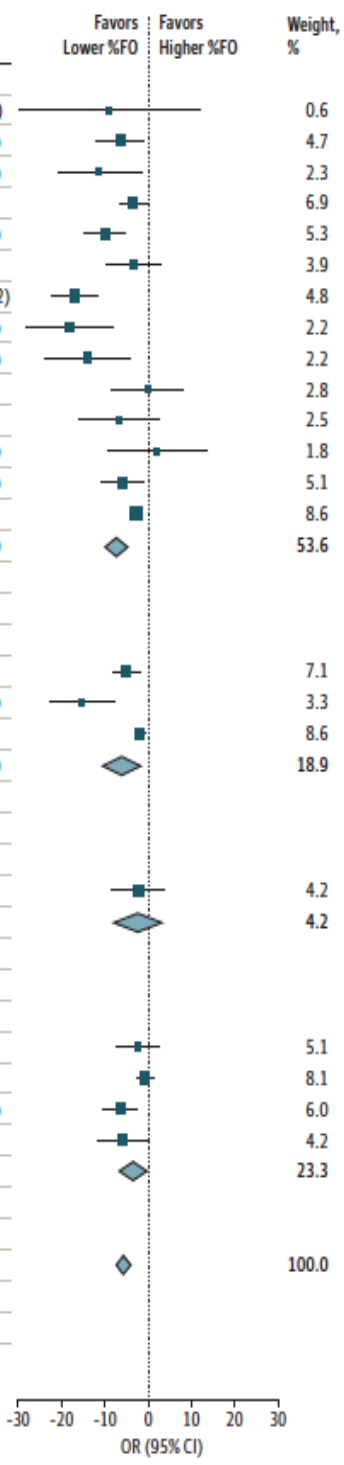


Included were 12 studies.[6,24,27,31,35,38,40,43,44,49,51,52] CRRT indicates continuous renal replacement therapy; %FO, percentage fluid overload; OR, odds ratio; and PICU, pediatric intensive care unit.

Figure 4.4:

Figure 3. Percentage Fluid Overload (Continuous Variable)

Source	Survivors Mean	SD	Total	Nonsurvivors Mean	SD	Total	Mean Difference (95% CI)	Weight, %
CRRT								
Goldstein et al,[7] 2001	16.40	13.80	9	25.40	32.90	12	-9.00 (-29.68 to 11.68)	0.6
Foland et al,[30] 2004	8.80	10.80	69	15.30	15.50	44	-6.50 (-11.74 to -1.26)	4.7
Goldstein et al,[32] 2005	14.20	15.90	60	25.40	32.90	56	-11.20 (-20.71 to -1.69)	2.3
Flores et al,[29] 2008	10.60	5.55	23	13.90	5.03	28	-3.30 (-6.24 to -0.36)	6.9
Hayes et al,[35] 2009	18.75	10.10	42	28.80	10.30	34	-10.05 (-14.67 to -5.43)	5.3
Elbahlawan et al,[28] 2010	1.45	6.90	5	4.90	3.65	25	-3.45 (-9.66 to 2.76)	3.9
Selewski et al,[8] 2011	8.00	8.80	50	25.00	18.50	63	-17.00 (-22.18 to -11.82)	4.8
Selewski et al,[49] 2012	20.10	16.30	18	38.30	18.50	35	-18.20 (-27.91 to -8.49)	2.2
Askenazi et al,[21] 2013	9.45	14.50	36	23.40	29.60	48	-13.95 (-23.57 to -4.33)	2.2
Boschee et al,[23] 2014	17.60	23.10	66	17.80	15.10	24	-0.20 (-8.42 to 8.02)	2.8
Jhang et al,[38] 2014	13.10	16.97	43	19.84	24.61	44	-6.74 (-15.61 to 2.13)	2.5
Gulla et al,[33] 2015	11.10	14.30	14	9.10	15.30	13	2.00 (-9.19 to -13.19)	1.8
Kaempfen et al,[39] 2017	6.15	7.56	41	12.20	11.76	30	-6.05 (-10.85 to -1.25)	5.1
Choi et al,[25] 2017	0.76	1.33	73	3.50	3.63	50	-2.74 (-3.79 to -1.69)	8.6
Subtotal (95% CI)			549			506	-7.21 (-10.08 to -4.33)	53.6
Heterogeneity: $\tau^2=17.57$; $\chi^2_8=55.19$, ($P<.001$); $I^2=76\%$								
Test for overall effect: $z=4.91$, ($P<.001$)								
Shock/sepsis								
Abulebda et al,[4] 2014	5.20	6.30	277	10.30	8.80	40	-5.10 (-7.93 to -2.27)	7.1
Bhaskar et al,[5] 2015	16.00	12.00	99	31.25	13.50	15	-15.25 (-22.48 to -8.02)	3.3
Chen et al,[24] 2016	0.78	1.97	141	2.68	4.08	61	-1.90 (-2.97 to -0.83)	8.6
Subtotal (95% CI)			517			116	-6.01 (-10.91 to -1.11)	18.9
Heterogeneity: $\tau^2=14.85$; $\chi^2_8=16.39$, ($P<.001$); $I^2=88\%$								
Test for overall effect: $z=2.40$, ($P=.02$)								
ALI								
Arikan et al,[20] 2012	13.70	10.00	66	15.90	10.30	14	-2.20 (-8.11 to 3.71)	4.2
Subtotal (95% CI)			66			14	-2.20 (-8.11 to 3.71)	4.2
Heterogeneity: Not applicable								
Test for overall effect: $z=0.73$, ($P=.47$)								
General								
Ketharanathan et al,[40] 2014	3.40	2.10	90	5.70	7.74	10	-2.30 (-7.12 to 2.52)	5.1
Sinitsky et al,[50] 2015	7.80	5.70	583	8.50	6.30	53	-0.70 (-2.46 to 1.06)	8.1
Sutawan et al,[52] 2016	1.40	8.20	60	7.90	12.90	60	-6.50 (-10.37 to -2.63)	6.0
Diaz et al,[26] 2017	12.70	13.80	189	18.40	16.60	35	-5.70 (-11.54 to 0.14)	4.2
Subtotal (95% CI)			922			158	-3.39 (-6.64 to -0.14)	23.3
Heterogeneity: $\tau^2=6.90$; $\chi^2_8=8.86$, ($P=.03$); $I^2=66\%$								
Test for overall effect: $z=2.04$, ($P=.04$)								
Total (95% CI)							-5.62 (-7.28 to -3.97)	100.0
Heterogeneity: $\tau^2=8.03$; $\chi^2_8=87.77$, ($P<.001$); $I^2=76\%$								
Test for overall effect: $z=6.66$, ($P<.001$)								
Test for subgroup differences: $\chi^2_8=4.14$, ($P=.25$); $I^2=27.6\%$								



Shown is the association with mortality, stratified by case mix. Included were 22 studies.[4,5,7,8,20,21,23-26,28-30,32,33,35,38-40,49,50,52] ALI indicates acute lung injury; CRRT, continuous renal replacement therapy; %FO, percentage fluid overload; and OR, odds ratio.

4.6 Appendix

eTable 4.1: List of conference proceedings searched

- The Society of Critical Care Medicine (SCCM)
- Canadian Critical Care Society
- The European Society of Intensive Care Medicine (ESICM)
- The International Symposium on Intensive Care and Emergency Medicine (ISICEM)
- The World Federation of Pediatric Intensive and Critical Care Societies
- American Society of Nephrology (ASN)
- International Society of Nephrology (ISN)
- International Symposium on AKI in Children
- International Conference on Pediatric Continuous Renal Replacement Therapy (pCRRT)

eTable 4.2: Newcastle-Ottawa quality assessment scale

1. Cohort studies

Newcastle-Ottawa Scale (Cohort Studies)										
		Selection				Comparability	Outcome			Total
Author and Year	Study Design	Representativeness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest	Comparability of cohorts	Assessment of outcome	Adequate duration of follow-up	Adequate follow-up of cohort	Total Score
Abulebda, 2014	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
Arikan, 2012	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Askenazi, 2013	PC	0	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	7
Baird, 2010	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	7
Boschee, 2014	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	7
Chen, 2016	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Choi, 2016	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
De Galasso, 2016	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Diaz, 2017	PC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Elbahlawan, 2010	RC	0	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	6
Flores, 2008	PC	0	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	6
Flori, 2011	PC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
Foland, 2004	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
Gillespie, 2004	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
Goldstein, 2005	PC	0	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	7
Goldstein, 2001	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
Gulla, 2015	RC	0	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	6
Hassinger, 2014	PC	1*	A (1*)	A (1*)	A (1*)	A (1) B (0)	A (1*)	A (1*)	A (1*)	8

Hayes, 2009	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Hazle, 2013	PC	0	A (1*)	A (1*)	A (1*)	A (1) B (1)	A (1*)	A (1*)	A (1*)	8
Inglese, 2017	RC	0	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	6
Jhang, 2014	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
Kaempfen, 2017	RC	0	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	6
Ketharanathan, 2014	PC	1*	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	7
Lex, 2016	PC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Li, 2016	PC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Lombel, 2012	RC	0	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	7
Michael, 2004	PC	0	A (1*)	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	6
Modem, 2014	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
Naveda, 2016	PC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Park, 2016	RC	0	A (1*)	A (1*)	A (1*)	A (1) B (0)	A (1*)	A (1*)	A (1*)	7
Randolph, 2005	PC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Sampaio, 2015	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Seguin, 2014	RC	1*	A (1*)	A (1*)	A (1*)	A (1) B (1*)	A (1*)	A (1*)	A (1*)	9
Selewski, 2011	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Selewski, 2012	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Sinitsky, 2015	RC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1)	A (1*)	A (1*)	A (1*)	8
Sutherland, 2010	PC	1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8
Valentine, 2012	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Vidal, 2016	RC	1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9

RC = retrospective cohort; PC= prospective cohort
For comparability: A is age, B is illness severity

2. Case Control studies

Newcastle-Ottawa Scale (Case control studies)										
		Selection				Comparability	Outcome			Total
Author and Year		Case definition adequate?	Representativeness of t cases	Selection of Controls	Definition of Controls	Comparability of cases and controls	Assessment of expsoure	Same method of ascertainment	Non-Response rate	Total Score
Bhaskar, 2015		1*	A (1*)	A (1*)	A (1*)	A (1*) B (1*)	A (1*)	A (1*)	A (1*)	9
Hoover, 2008		1*	0	A (1*)	A (1*)	A (0) B (0)	A (1*)	A (1*)	A (1*)	6
Sutawan, 2016		1*	A (1*)	A (1*)	A (1*)	A (0) B (1*)	A (1*)	A (1*)	A (1*)	8

For comparability: A is age, B is illness severity

eTable 4.3: Fluid balance assessment methods

Main Fluid Balance Measure	Assessment Period		Paper(s)
	Start	End	
Percent Fluid Overload (FO%) (intake-output based)	PICU admission	24 hours	Chen, 2016 Li, 2016 Hassinger, 2014
		48 hours	Sinitsky, 2015 Vidal, 2016
		72 hours	Hazle, 2013
		7 days	Abulebda, 2014 Bhaskar,2015 Sampaio, 2015
		14 days	Arikan, 2012
		PICU discharge	Diaz, 2017 Ketharanathan, 2014 Michael, 2004 Naveda, 2016 Sutawan, 2016
		CRRT initiation	Askenazi, 2013 Boschee, 2014 de Galasso, 2016 Flores, 2008 Gillespie, 2004 Goldstein,2001 Goldstein, 2005 Gulla, 2015 Hayes, 2009 Jhang, 2014 Kaempfen, 2017 Lombel, 2012 Modem, 2014 Selewski, 2011 Sutherland, 2010
	24 hours before CRRT initiation		Elbahlawan, 2010 Choi, 2017
	7 days before CRRT initiation		Baird, 2010 Foland, 2004
	Intra-operative	48 hours	Lex, 2016
		72 hours	Park, 2016
		PICU discharge	Seguin, 2014
Percent Fluid Overload FO% (weight based)	PICU admission	7 days	Hazle, 2013
		CRRT initiation	Lombel, 2012 Selewski, 2011 Selewski, 2012
Net Fluid Balance (ml/kg)	PICU admission	7 days	Valentine, 2012
		PICU discharge	Inglese, 2017
	Intubation	Extubation	Randolph, 2005
	Onset of ALI	72 hours post ALI	Flori, 2011
	ECMO start	ECMO end	Hoover, 2008
Net Fluid Balance (L/m^2)	PICU admission	7 days	Willson, 2013

eTable 4.4: Weights used in FO definitions

Weight used	Paper (s)
PICU admission weight	Chen, 2016 Choi, 2017 Diaz, 2017 LI, 2016 Abulebda, 2014 Bhaskar,2015 Arikan, 2012 Askenazi, 2013 Boschee, 2014 de Galasso, 2016 Flores, 2008 Gillespie, 2004 Goldstein,2001 Goldstein, 2005 Gulla, 2015 Jhang, 2014 Ketharanathan, 2014 Lombel, 2012 Modem, 2014 Selewski, 2011 Sutherland, 2010 Sutawan, 2016
Hospital admission weight	Hayes, 2009 Lombel, 2012 Michael, 2004 Selewski, 2011 Selewski, 2012 Baird, 2010 Sinitsky, 2015
Hospital admission weight or the most recent available PICU weight	Lex, 2016
The lowest patient weight from either hospital admission or the most recent within 1 month of admission	Foland,2004
PICU dry or ideal bodyweight *	Lombel, 2012 Randolph, 2005
Outpatient weight	Hazle, 2013 Lombel, 2012
Not specified	Elbahlawan, 2010 Flori, 2011 Hassinger, 2014 Hoover, 2008 Inglese, 2017 Kaempfen, 2017 Naveda, 2016 Park, 2016 Sampaio, 2015 Seguin, 2014 Valentine, 2012 Vidal, 2016 Willson, 2013

* Randolph et al used "ideal body weight": Estimated as the 50th percentile for recumbent length and sex from the National Center for Health Statistics growth charts.
* Lombel et al used "PICU dry weight": assigned at the time of PICU admission by the PICU staff based on clinical judgment of pre-morbid weight

eTable 4.5: Studies reporting respiratory dysfunction and outcomes

Study	Population	Main Respiratory Outcomes
Arikan, 2012	Multisystem (ventilated only)	• Peak %FO correlated significantly with peak OI (r = 0.26, p < 0.02) • Higher peak %FO was an independent predictor of higher peak OI (p = 0.009) on multivariate regression analysis • Daily %FO >15% was independently associated with that day's OI (regression coefficient= 0.12, p = 0.004) • %FO and OI regression coefficient progressively increased with increased %FO cut-off • %FO>15% was independently associated with longer duration of MV (OR 0.46, p =0.01)
Bhaskar, 2015	Sepsis/shock	• MV was longer in patients with FO (median 2 vs 6 days, p = 0.004). However, the difference was not significant in matched analysis (5 vs 6 days, p = 0.36)
Elbahlawan, 2010	Stem cell transplant on CRRT	• Improvement of PaO2/FiO2 correlated significantly with reduction of fluid balance after initiation of CRRT (median PaO2/FiO2 increase of 30.51 after 24 hours, and 43 after 48 hours, p <0.05)
Flori, 2011	ALI	• Positive fluid balance (in 10 mL/kg/day increments) was independently associated with fewer ventilator-free days (regression coefficient = – 0.21, p = 0.02)
Hassinger, 2014	Post cardiac surgery	• Early FO was associated with prolonged MV (43% vs 8.8%). However, the association was not significant after adjusting for severity of illness (OR 3.15, p = 0.18)
Hayes, 2009	CRRT	• Higher %FO was associated with longer MV (median 7 vs 16 days, p = 0.02). The association was not significant on multivariable regression.
Ketharanathan, 2014	Multisystem	• %FO correlated significantly with OI (r = 0.33, p = 0.01) and length of MV (r = 0.34, p < 0.001)
Lex, 2016	Post cardiac surgery	• Higher %FO was independently associated with prolonged MV (OR 1.01, p = 0.03)
Li, 2016	Multisystem	• There was a trend towards prolonged MV in the early FO group but it was not significant statistically (26.6% vs 17%, p = 0.07)
Sampaio, 2015	Post cardiac surgery	• %FO was independently associated with Length of MV in multiple linear regression (p < 0.01) • Peak %FO correlated significantly with maximum OI (Spearman's test = 0.37, p = 0.01) • Peak %FO was associated with chest wall edema (p = 0.003) and pleural effusion (p = 0.01) • Peak %FO was not associated with extubation failure (p = 0.98)
Seguin, 2014	Post cardiac Surgery	• Peak %FO correlated significantly with maximum OI (r = 0.32, p = 0.001) • Higher FO % was independently associated with worse OI (HR 0.16, p = 0.03) • %FO at day 2 was independently associated with length of mechanical ventilation (HR 0.97, p = 0.03)
Study	**Population**	**Main Respiratory Outcomes**

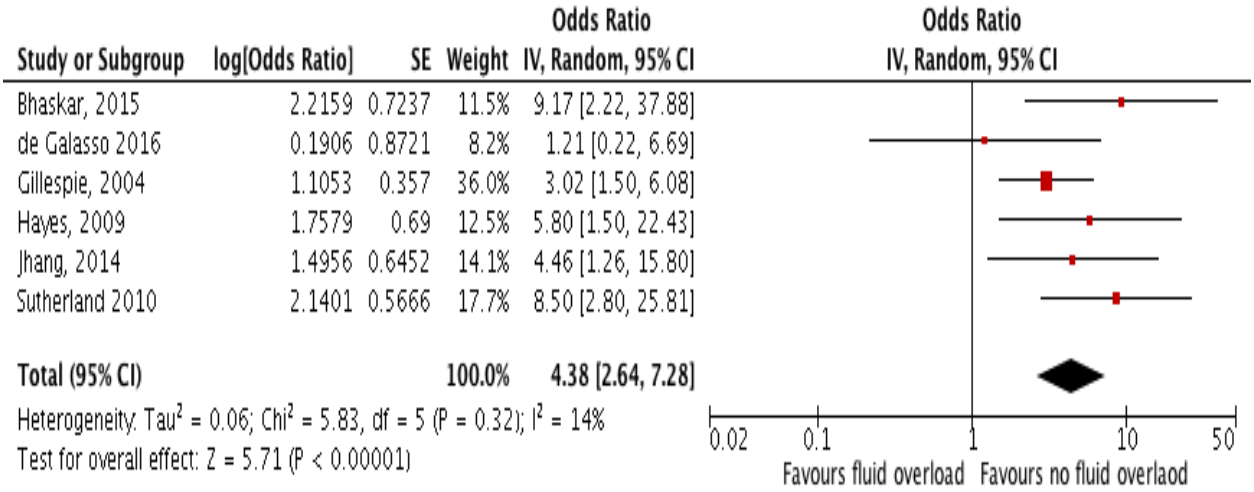
Sinitsky, 2015	Multisystem	• %FO correlated significantly with oxygenation index (Spearman's test = 0.32, $p < 0.001$) and with length of MV (Spearman's test = 0.27; $p < 0.001$) • %FO was independently associated with OI at 48 hours (regression coefficient 0.26, $p < 0.001$) • %FO was independently associated with MV days (regression coefficient 0.14, $p = 0.002$)
Valentine, 2012	ALI	• Higher fluid balance (mL/kg/day) at day 3 was independently associated with fewer ventilator-free days (regression coefficient= -0.02, $p = 0.01$)
Wilson, 2013	ALI	• Higher fluid balance (L/m^2) was associated with fewer ventilation-free days ($p <0.001$) • Fluid balance (L/m^2) was independently associated with OI (regression coefficient 0.52, $p =0.01$)
Randolph, 2005	Multisystem (ventilated only)	• Higher fluid balance (ml/kg/day) was associated with nonsignificant trend towards longer duration of ventilation weaning (HR 0.94, $P = 0.051$) • Positive fluid balance did not predict extubation failure
Chen, 2016	Sepsis	• Early FO was an independent predictor for the need of MV (OR 1.2, $p =0.04$) • However, FO was not associated with the duration of MV ($p = 0.3$)
Diaz, 2017	Multisystem	• Peak %FO correlated with length of MV ($r = 0.67$, $p < 0.01$)
Inglese, 2017	Multisystem (ventilated only)	• Fluid balance (mL/kg/day) on day 3 was independently associated with duration of MV ($p = 0.048$), but not with OI
Vidal, 2016	Multisystem (ventilated only)	• FO was associated with prolonged MV (OR 4.02, $p = 0.04$). However, the association was not significant after adjusting for severity of illness (OR 3.7, $p = 0.06$)

OI = Oxygenation index
MV = Mechanical ventilation
ALI = Acute lung injury
OR = Odds ratio
HR = Hazard ratio

eTable 4.6: Other outcomes from individual studies

Study	Outcome	Result
Abulebda 2014	Composite of "complicated course": death within the 28-day study period or persistence of >2 organ failures at day-7 post admission.	• Those with complicated course had higher %FO (8.5% Vs 3.8%, P <0.001)
Bhaskar 2015	ECMO use	• FO group had more ECMO use compared to no FO (OR 6.2, P=0.01)
Hassinger 2014	Hemodynamic variables	In FO group: • Later first inotrope-free day (day 5 Vs day 3, P <0.001) • Higher peak inotropic score (P <0.01) • More likely to have escalation in inotropic support (20% vs 4.4%) (p = 0.01)
Hazle 2013	Composite of poor outcome: need for CRRT, upper quartile time to first extubation or intensive care length of stay, or death within 30 days of surgery	• Maximum %FO was higher in patients who developed "poor outcome" (24% vs 14%, p=0.02)
Lex 2016	Post cardiac bypass low cardiac output syndrome	• Cumulative %FO on day of surgery was independently associated with low cardiac output syndrome (OR 1.21, P= 0.002)

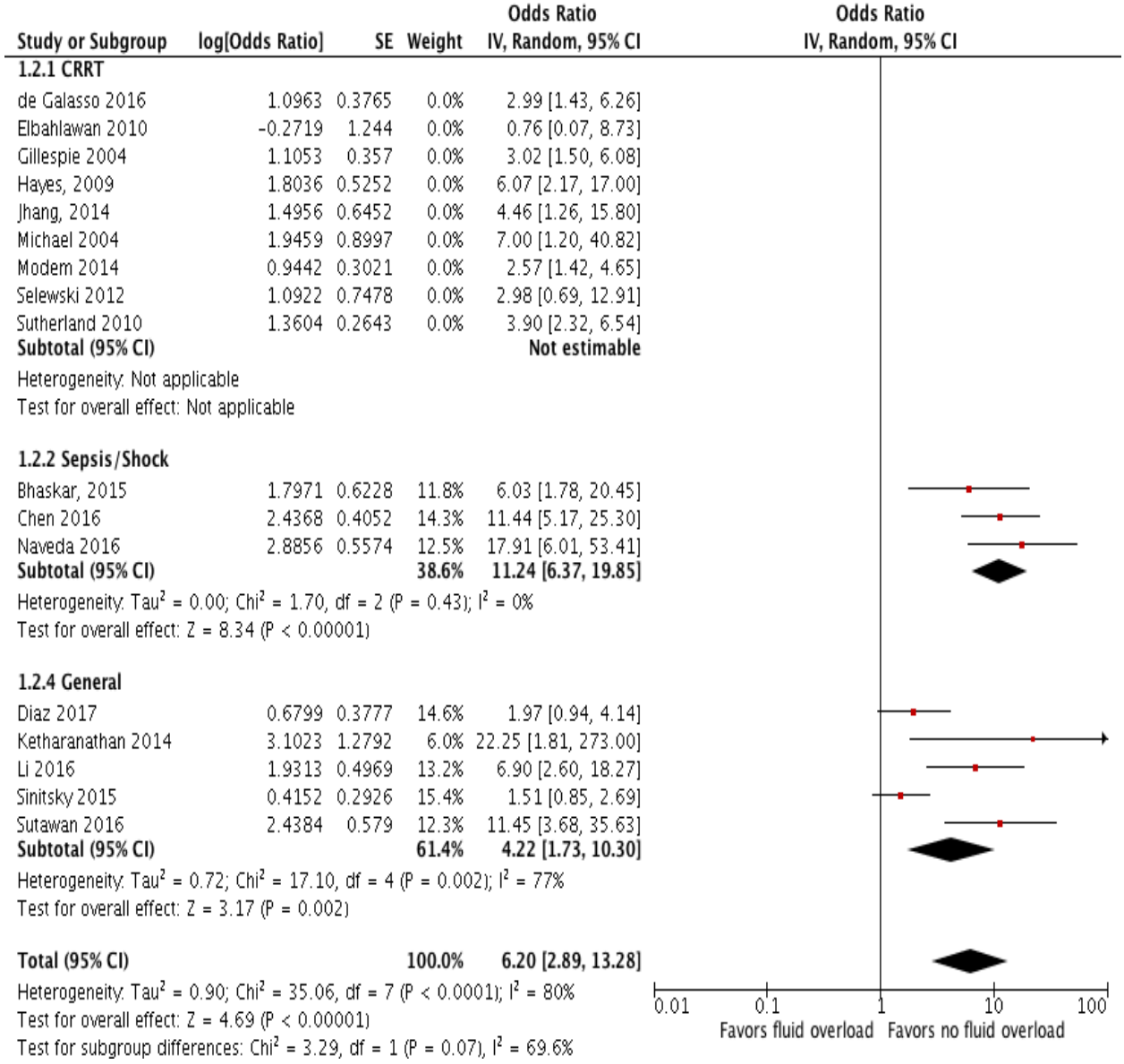
eFigure 4.1: Association between FO (categorical exposure) and mortality in studies adjusting for severity of illness



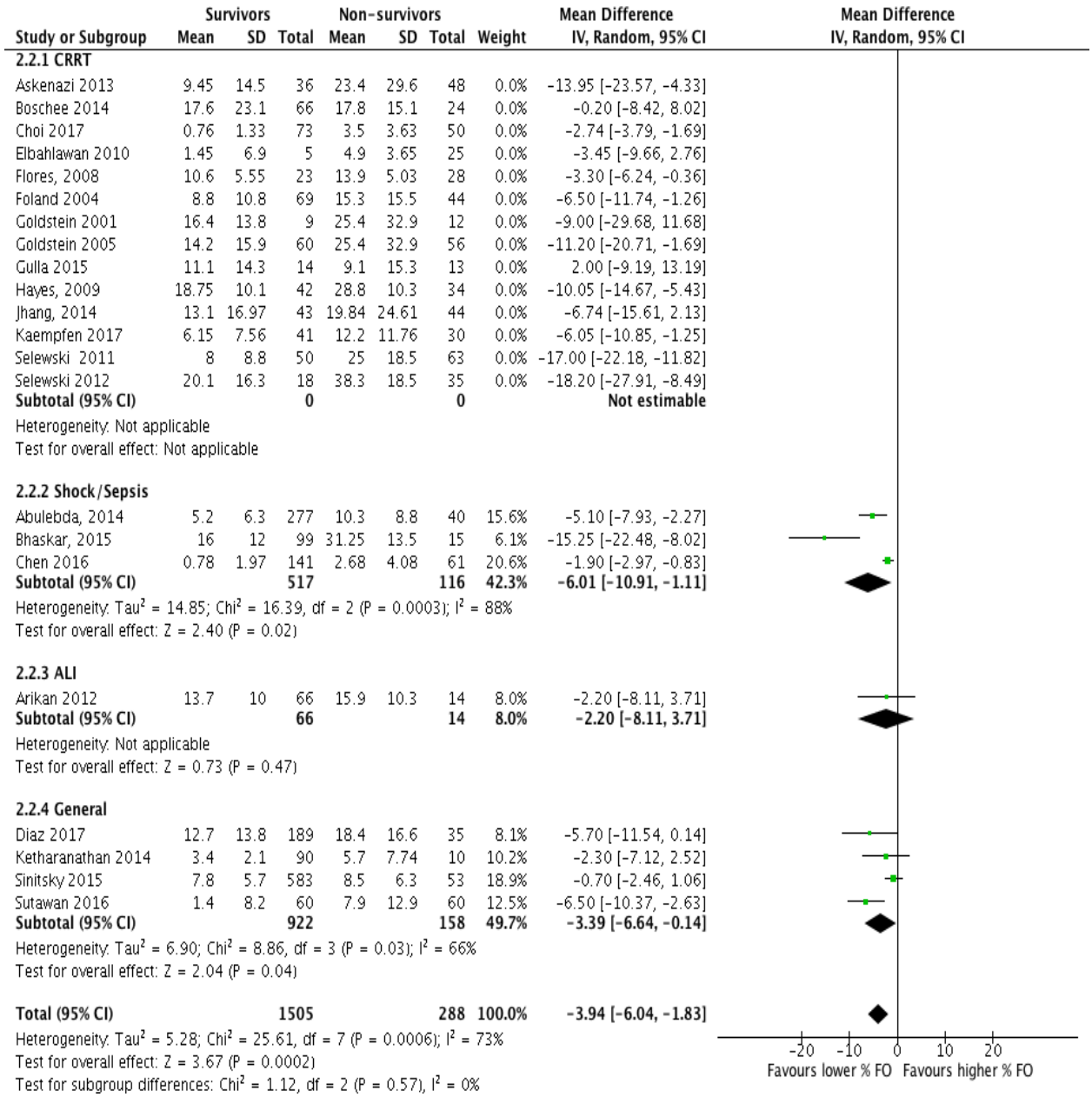
Studies adjusted for:

- Bhaskar, 2015: PIM 2, age, indication for ICU admission, duration of hospitalization prior to ICU transfer, presence of infectious diagnoses, presence of oncologic disease(s), presence of respiratory failure, need for vasopressor support and presence of renal dysfunction.
- De Glasso, 2016: PIM2, diagnosis, MODS at CRRT initiation, hypotension at CRRT initiation
- Gillespie, 2004: PRISM2, dose of CVVH replacement of fluid, number of inotropes
- Hayes, 2009: PRISM 2, age, race, sex
- Jhang, 2014: SOFA score
- Sutherland, 2010: PRISM, MODS, CRRT modality, number of inotropes

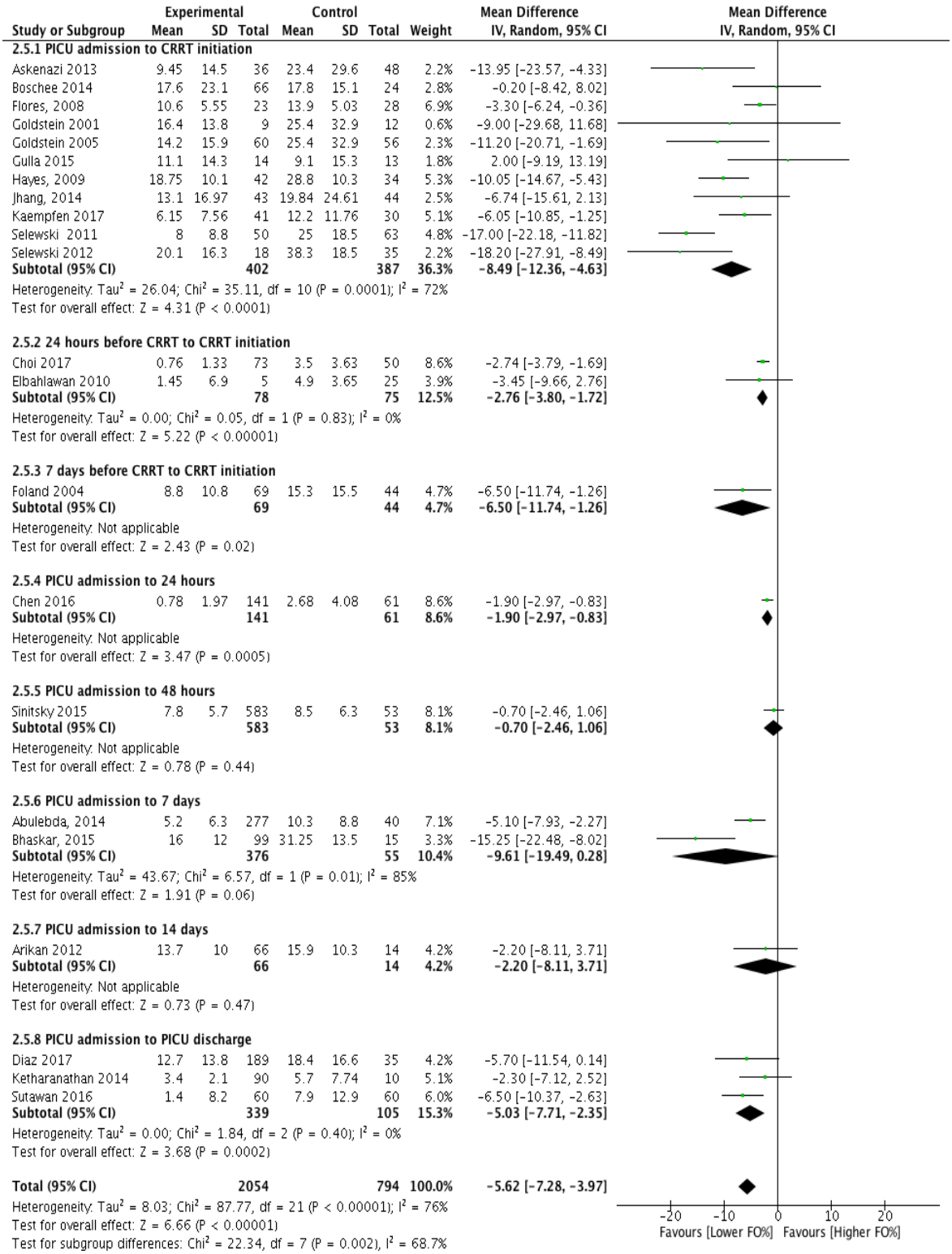
eFigure 4.2: Association between fluid overload (categorical exposure) and mortality omitting studies of children receiving CRRT



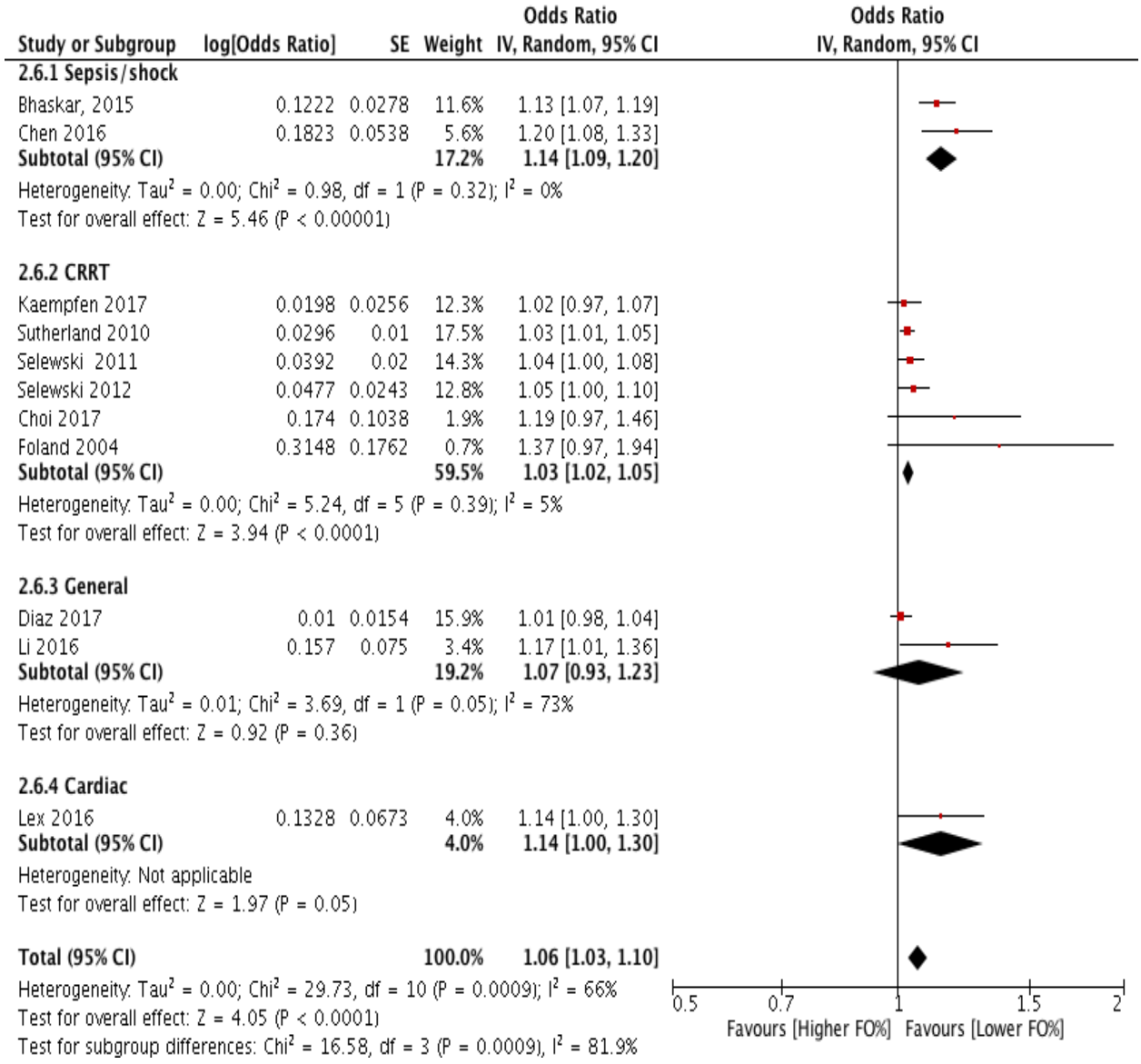
Association between fluid overload (continuous exposure) and mortality omitting studies of children receiving CRRT



eFigure 4.3: Percent fluid overload (%FO) (continuous variable) association with mortality, stratified by assessment period



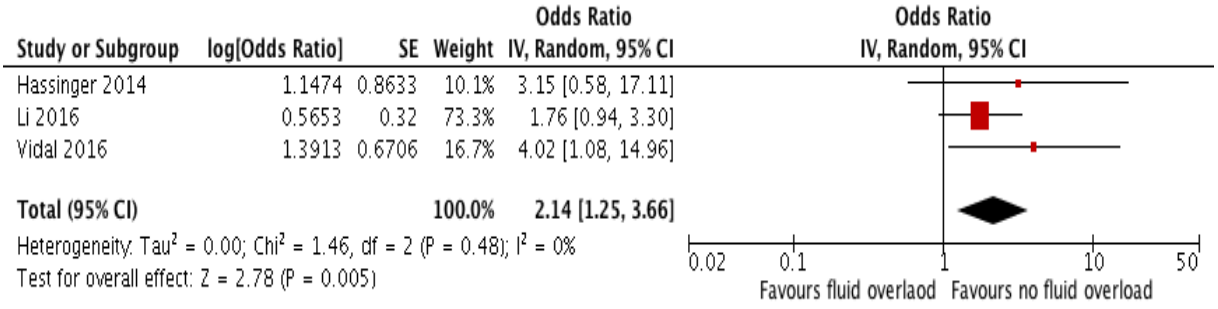
eFigure 4.4: Percent fluid overload (%FO) (continuous variable) association with mortality in studies adjusting for severity of illness (stratified by case-mix)



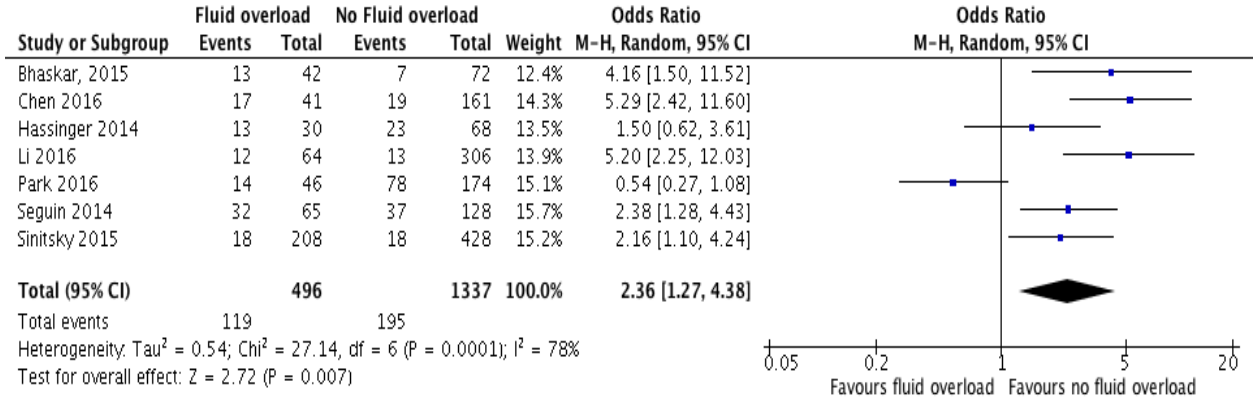
Studies adjusted for:

- Bhaskar, 2015: PIM 2, age, indication for ICU admission, duration of hospitalization prior to ICU transfer, presence of infectious diagnoses, presence of oncologic disease(s), presence of respiratory failure, need for vasopressor support and presence of renal dysfunction.
- Chen, 2016: PIM2, age
- Kaempfen, 2017: Weight, length of stay prior to CRRT, inotrope need, mean blood pressure prior to CRRT
- Sutherland, 2010: PRISM, MODS, CRRT modality, number of inotropes
- Selewski, 2011: Age, hospital days pre CRRT, extracorporeal life support status, pRIFLE status, and number of vasoactive agents
- Selewski, 2012: Age, PRISM
- Choi, 2017: PRISM III, inotrope score, length of PICU stay, length of stay prior to CRRT, duration of CRRT, lactic acid, Creatinine, Urea
- Foland, 2004: PRISM III
- Diaz, 2017: PRISM II, age, AKI status, vasoactive support, >3 organ failure
- Li, 2016: PRISM III, age, need for mechanical ventilation, AKI
- Lex, 2016: age, emergency operation, cardiac bypass time, CRRT, low cardiac output syndrome

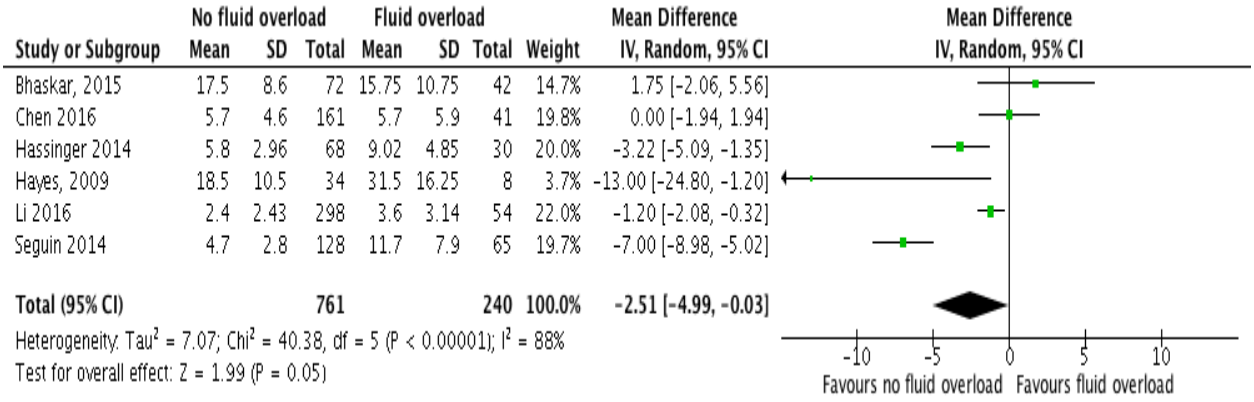
eFigure 4.5: Random-Effects Meta-analysis of FO and prolonged mechanical ventilation



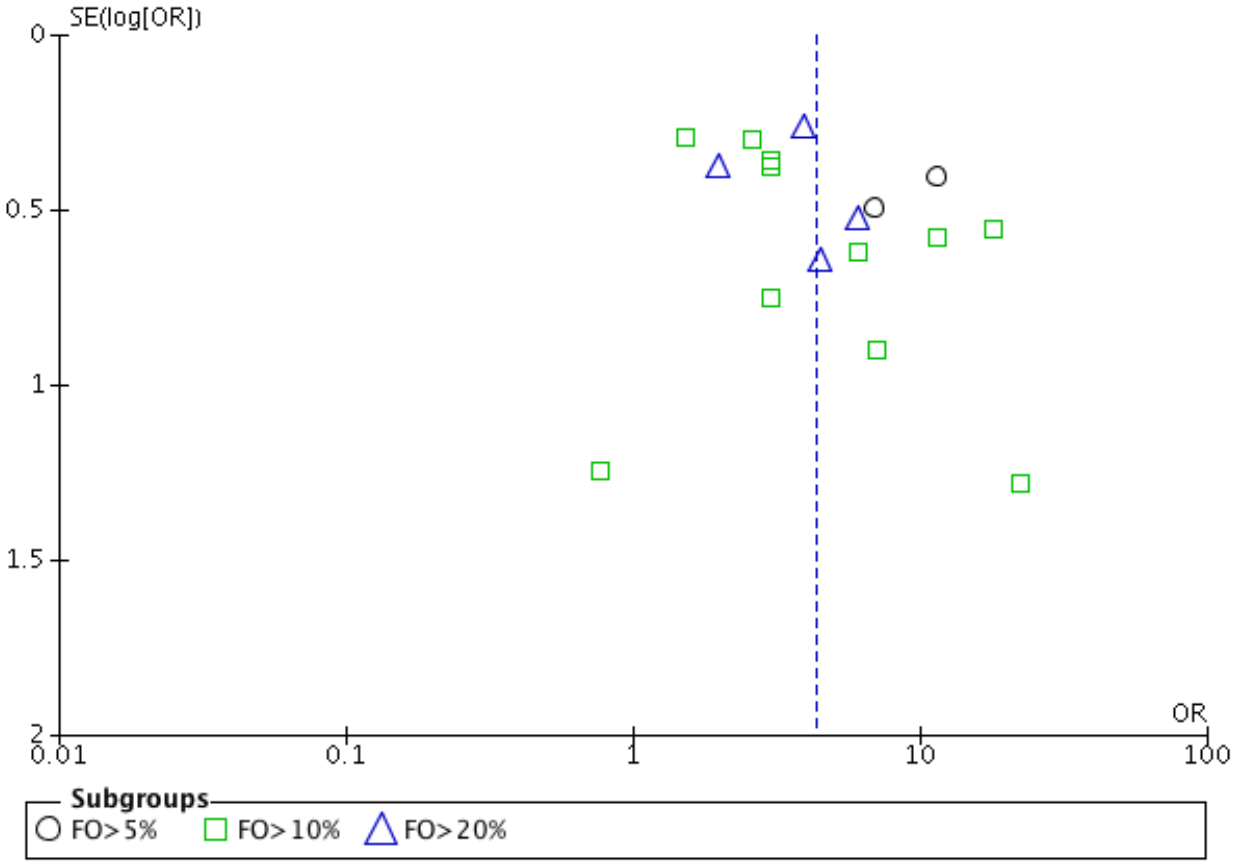
eFigure 4.6: Random-Effects Meta-analysis of FO and acute kidney injury



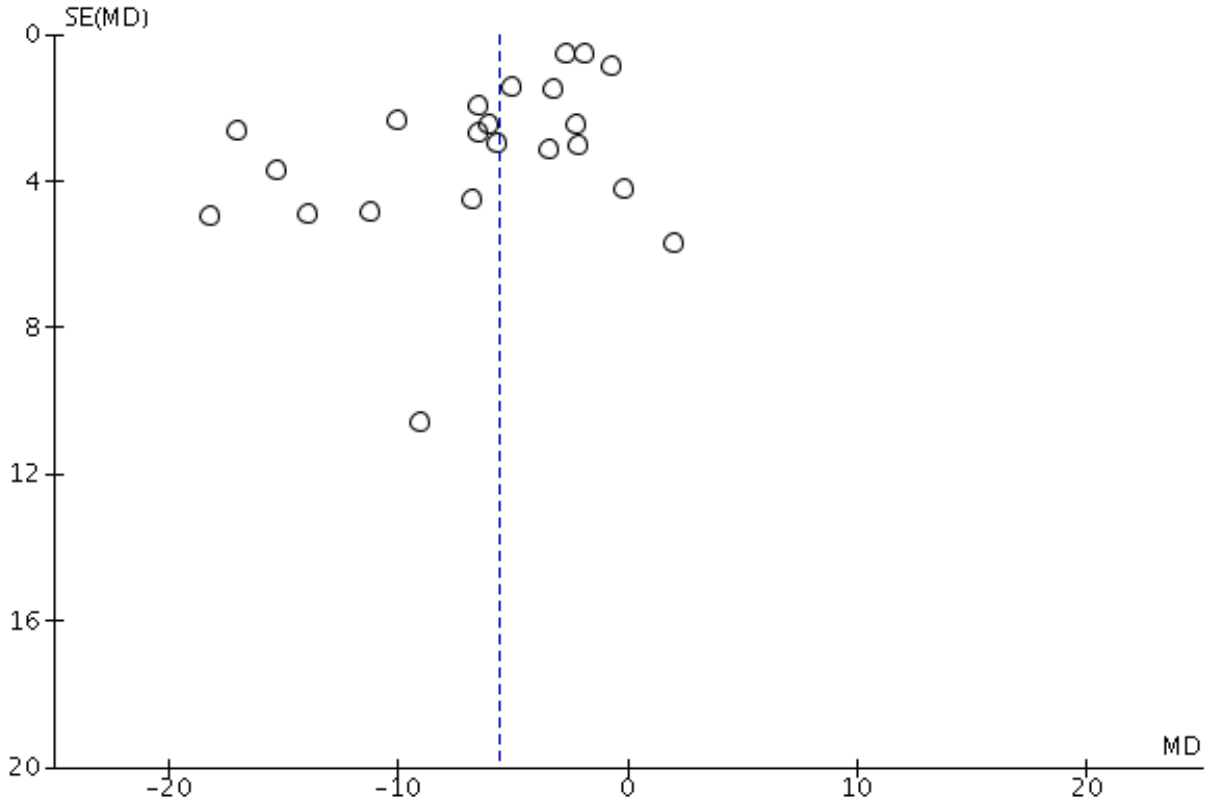
eFigure 4.7: Random-Effects Meta-analysis of FO and PICU length of stay



eFigure 4.8: Funnel plot of FO Odds of mortality (categorical exposure) analysis



eFigure 4.9: Funnel plot of fluid overload percent (%FO) (continuous variable) association with mortality analysis



CHAPTER 5

Conclusion

5.1 Summary of The Results

My thesis reports findings from two studies: first, a population-based cohort study describing the epidemiology, risk factors and outcomes of AKI in critically ill children. Second, a systematic-review and meta-analysis evaluating the association between fluid balance and outcomes in critically ill children.

The first study described the population-level epidemiology and outcomes for critically ill children with AKI. AKI was common, occurring in an estimated 30% of the PICU patients, with annual incidence rate of 34 per 100,000 children. Severe AKI was independently associated with greater risk of short and longer-term mortality and other important secondary outcomes, including longer receipt of mechanical ventilation and vasoactive support, and prolonged PICU and hospital stay. In addition, severe AKI patients were at increased risk of death beyond discharge from hospital, adding to the overall burden potentially attributable to AKI.

The study findings show that critically ill children who are younger than 1 year tended to be at higher risk of developing AKI and may represent a future target population for greater surveillance, earlier intervention or the focus of preventive strategies. In addition, the study identified three clinical factors associated with the development of severe AKI including severity of illness, the receipt for vasoactive support and fluid overload. Of these, fluid overload may be potentially modifiable and a target for interventional strategies.

In the second study, the systematic review and meta-analysis explored the association between fluid balance and outcomes in critically ill children, including AKI. The findings were robust and consistent in suggesting that fluid overload was common and portended greater risk for death, AKI, worsened respiratory function, and additional outcomes implying greater intensification of support. The study identified two clinically useful methods of assessing fluid balance based either on recorded daily intake-output or serial weight measurements. In addition, the findings identified four common definitions of fluid overload which showed significant association with outcomes: 1) Early fluid overload: cumulative percent fluid overload >5% in the first 24 hours. 2) Peak percent fluid overload >10% during PICU admission. 3) Cumulative percent fluid overload >10% at CRRT initiation. 4) Cumulative percent fluid overload >20% at CRRT initiation.

5.2 Strengths and Limitations

To my knowledge, no pediatric study has described the population-level incidence of AKI among critically ill children. The incidence and associated outcomes of AKI in this study were similar to those described in AWARE, the largest pediatric AKI study. This consistency in findings between the two studies extends confidence in the estimates reported in AWARE and suggests that KDIGO criteria is robust for discriminating clinically relevant outcomes in pediatric populations. The study described the impact of AKI on long term mortality, which has not been commonly reported in earlier pediatric AKI studies. The study is also strengthened by the use of pre-specified protocol and the utilization of prospectively electronically collected data with no missing data points. The data were obtained from 3 different PICUs with variable

practices and processes of care increasing the generalizability of the findings. The population-based nature and inclusion of all patients in a geographically defined area governed by a single health system minimizes the risk of selection bias while providing robust estimates of disease burden. Moreover, unlike prior work, I was able to evaluate patients for AKI during the entire PICU stay.

The systematic review is strengthened by employing a comprehensive search strategy, by rigorous screening and eligibility criteria, and by transparent reporting of the findings. The primary and secondary outcome findings were robust in sensitivity analyses considering pre-specified case-mix subgroups, variable fluid overload definitions and after including only studies where illness severity adjustment was possible

Both studies have limitations that warrant discussion. The first study is observational in design and as such I cannot definitively confirm the causal relationship between AKI and clinical outcomes. The population-based incidence of all pediatric AKI cases occurring in hospital cannot be determined, considering the study only included patients admitted to PICU. Despite adjusting for severity of illness and other important potential confounders, the retrospective design limited the ability to account for important interventions such as exposure to nephrotoxins or the use of diuretics. This could partly explain the observed variable AKI incidence between centres. The baseline SCr was not known in about half of the patients. Similar figures have been described in other pediatric studies and can be explained by the fact that majority of children have no comorbidities that necessitate evaluating SCr in the community. Nevertheless, this could be a source of classification bias. When those patients were excluded, the incidence of AKI was

higher but the association with mortality was unchanged. Finally, the fluid deficit state and fluid given prior to PICU admission were not available for the calculations of fluid overload, which might have resulted in misclassification.

The studies included in the systematic review have important limitations. First, nearly all studies were observational, mostly retrospective with many having limited capacity for adjustment, and therefore are at risk of selection bias and residual confounding. Second, as such, I cannot definitively confirm the causal link between fluid overload and adverse outcomes given the paucity of rigorous experimental trials evaluating fluid management strategies in critically ill children. Third, studies included had wide variation in case-mix and in operational definitions for fluid balance and fluid overload, and significant heterogeneity in outcomes which limited the capacity for pooled analyses in selected circumstances. Moreover, selected studies reported fluid overload as continuous exposure using median and range necessitating transformation of the data to mean and standard deviation using previously described formulas. This may have contributed to imprecise effect estimates. Some PICU sub-populations, such as trauma and burn patients were underrepresented in the included studies which could limit the generalizability of the findings. Few studies evaluated the temporal changes in fluid balance during PICU course. Finally, none of the included studies considered the potential fluid deficit state of children or accounted for fluid administration and accumulation prior to PICU admission. This may have contributed to misclassification of fluid overload, when considering many PICU patients receive fluid resuscitation pre-hospital, in the emergency department, operating theatre or on general wards prior to transfer to PICU.

5.3 Concluding Statement

My thesis provides evidence that AKI is common in critically ill children and portends worse outcomes, including greater mortality and health care resource utilization. AKI therefore represents an important burden for health care. These findings highlight the need for improved detection of AKI and for efforts to improve care for these patients. This can include addressing potentially modifiable risk factors such as fluid overload. Putting it all together, the thesis findings provides a foundation for development of optimal strategies for fluid management among critically ill children with or at risk of AKI, specifically in the form of rigorous clinical trials, aimed specifically at avoiding and mitigating iatrogenic or avoidable fluid overload.

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