JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2024, VOL 7, NO S12

The Management of Metabolic Acidosis in Critical Illness: A Systematic Review

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Abstract

Background:

Metabolic acidosis is a critical condition frequently encountered in intensive care units (ICUs), with diverse etiologies and associated comorbidities that significantly influence patient outcomes. This systematic review evaluates the prevalence and impact of common comorbidities, including chronic hypertension, diabetes mellitus, chronic kidney disease (CKD), sepsis, and respiratory and liver diseases, in critically ill patients with metabolic acidosis.

Methods: A comprehensive literature search was conducted using major databases to identify studies published between 2016 and 2024 that examined critical care patients with metabolic acidosis. Data on associated diseases and clinical parameters such as serum bicarbonate, potassium, creatinine levels, Sequential Organ Failure Assessment (SOFA) scores, and estimated glomerular filtration rates (eGFR) were extracted. Forest plots were generated to summarize the findings and visualize inter-study variability.

Results: The review included 40 studies encompassing a diverse critical care population. Chronic hypertension (18–98.3%), CKD (up to 49%), and sepsis (up to 89.5%) were the most frequently reported comorbidities. Chronic respiratory diseases (up to 46%) and liver diseases (up to 24.8%) were also significant contributors. CKD emerged as a predominant factor influencing the severity of metabolic acidosis, with a strong association between impaired renal function and worse outcomes. Comorbidities such as diabetes mellitus, particularly type 2 diabetes (up to 50.9%), further exacerbated acidosis through associated complications like diabetic ketoacidosis. Patients with sepsis demonstrated a higher prevalence of multiorgan dysfunction and lactic acidosis, resulting in increased mortality.

Conclusions: This review highlights the high prevalence and significant impact of comorbidities in critically ill patients with metabolic acidosis. The findings emphasize the need for individualized, multidisciplinary approaches targeting the complex interplay of comorbid conditions and acidosis. Early identification and management of key contributors, such as CKD and sepsis, are critical to improving patient outcomes. Further research is needed to develop precise therapeutic interventions for this high-risk population.

Keywords: Metabolic acidosis, critical care, chronic kidney disease, sepsis, hypertension, diabetes mellitus, comorbidities

Introduction

Background

Metabolic acidosis is a common acid-base disturbance characterized by a primary reduction in serum bicarbonate (HCO_3^-), leading to decreased blood pH (<7.35) (Kraut & Madias, 2010). This condition can arise from an increase in endogenous acid production (e.g., lactic acidosis or ketoacidosis), impaired acid excretion (e.g., renal failure), or bicarbonate losses (e.g., diarrhoea) (Schoolwerth et al., 2016; Wagner et al., 2019). In critically ill patients, metabolic acidosis is often multifactorial and reflects underlying pathologies such as sepsis, shock, or organ dysfunction, making its presence a significant marker of severity (Gao et al., 2019). This disturbance frequently correlates with hemodynamic instability, organ dysfunction, and an

increased risk of mortality, underscoring its clinical relevance in intensive care units (ICUs) (Easter, 2024; Ricci et al., 2024).

Acidosis imposes profound physiological stress on critical systems. Severe acidemia (pH <7.2) can compromise cardiovascular function by reducing myocardial contractility, impairing vascular tone, and exacerbating arrhythmias (Mitchell et al., 1972; Whitmore & Gunnerson, 2020). It also affects oxygen delivery and utilization, as shifts in the oxygen-hemoglobin dissociation curve can reduce tissue oxygenation (Rudinsky & Meadow, 1992). Furthermore, metabolic acidosis impairs enzymatic reactions and promotes inflammation, further worsening organ dysfunction (Kraut & Madias, 2010, 2012). Renal and respiratory systems are frequently taxed as compensatory mechanisms, potentially precipitating secondary complications such as hyperkalemia or respiratory fatigue (Matyukhin et al., 2020; Wesson et al., 2020). These cascading effects make timely and effective management of acidosis pivotal to improving clinical outcomes.

Despite its clinical importance, the management of metabolic acidosis in critical illness remains controversial. Diverse therapeutic approaches exist, including buffering agents like sodium bicarbonate, dialysis-based therapies, and fluid management strategies (Joannidis et al., 2011; Tamargo et al., 2024). However, their indications, timing, and impact on patient outcomes are debated. For instance, while sodium bicarbonate can rapidly correct pH, concerns persist about its efficacy in improving survival or organ function, and potential adverse effects like hypernatremia or fluid overload complicate its use (Haines et al., 2019). Similarly, the role of renal replacement therapies in addressing acidosis versus other complications is not clearly delineated (Forsythe & Schmidt, 2000). These uncertainties are compounded by variability in clinical guidelines, institutional practices, and patient responses.

The objective of this systematic review is to evaluate the role of acidosis management in critical care settings by analyzing its impact on clinical outcomes, including kidney function, associated co-morbidities, and mortality rates. Specifically, the review aims to:

1. Compare the efficacy and safety of various therapeutic approaches in managing metabolic acidosis.
2. Assess the implications of acidosis management on kidney-related outcomes, including estimated glomerular filtration rate (eGFR), serum bicarbonate levels, and other renal biomarkers.
3. Examine the prevalence of co-morbidities such as sepsis, chronic kidney disease, hypertension, and diabetes among critically ill patients undergoing acidosis management.
4. Provide insights into the clinical relevance of acidosis management strategies in improving overall survival and minimizing complications in critically ill populations.

A systematic review is necessary to synthesize the available evidence, identify effective management strategies, and clarify their impacts on critically ill patients. By addressing these knowledge gaps, this review aims to provide clinicians with evidence-based recommendations to improve patient care while highlighting areas for future research.

Pathophysiology of Metabolic Acidosis in Critical Illness

Metabolic acidosis in critically ill patients is a common and multifactorial condition, typically resulting from either an increased acid load, decreased acid excretion, or bicarbonate losses. The primary types of metabolic acidosis encountered in intensive care settings include:

Lactic Acidosis

Lactic acidosis arises from the overproduction or impaired clearance of lactic acid, often due to tissue hypoxia or mitochondrial dysfunction (Gómez & Mizock, 2019). Common causes include septic shock, cardiogenic shock, and hypovolemia, where impaired perfusion leads to anaerobic metabolism. Medications such as metformin or toxins like cyanide can also impair lactate metabolism, contributing to this type of acidosis (Luft, 2001).

Renal Tubular Acidosis (RTA)

RTA results from defects in renal acid handling, either in the proximal tubule (impaired bicarbonate reabsorption) or the distal tubule (impaired hydrogen ion excretion) (Reddy, 2011). In critically ill patients, acute kidney injury (AKI) is a more frequent contributor to acidosis,

with the kidneys failing to excrete acid loads effectively (Kunchur et al., 2024; Palmer et al., 2021).

Hyperchloremic Acidosis

This occurs secondary to an increase in chloride concentration, often associated with the administration of large volumes of normal saline during fluid resuscitation. The resulting acidosis is due to the dilutional reduction of bicarbonate concentration rather than an increase in acid production (Story et al., 2006).

Ketoacidosis

Ketoacidosis develops from the accumulation of ketone bodies, commonly in patients with diabetic ketoacidosis (DKA) (Fedorovich et al., 2013). It can also occur in alcoholic or starvation states when carbohydrate availability is low, leading to fatty acid metabolism for energy (Umpierrez & Kitabchi, 2003).

Correlation of Acid-Base Disturbances with Clinical Outcomes

Metabolic acidosis significantly influences the prognosis of critically ill patients. Severe acidemia (pH <7.2) has been associated with adverse physiological effects, which can escalate morbidity and mortality, as follows.

Cardiovascular Effects

Acidosis depresses myocardial contractility and reduces cardiac output, leading to compromised tissue perfusion (Walley et al., 1990). It also impairs vascular responsiveness to catecholamines, exacerbating hypotension in shock states. These effects can contribute to the progression of multi-organ failure (Rodríguez-Villar et al., 2021).

Renal and Electrolyte Disturbances

Acidosis impacts renal function by promoting hyperkalemia, a potentially life-threatening condition. It also increases calcium mobilization from bones, which can contribute to osteoporosis over time (Kim, 2021).

Inflammatory and Metabolic Dysregulation

Acidosis promotes inflammation and alters cellular metabolism, exacerbating conditions such as sepsis. It also impairs glucose utilization and protein synthesis, which can hinder recovery and wound healing (Matyukhin et al., 2020; Shoemaker, 2020).

Methodology

Search Strategy

A systematic and comprehensive search strategy was employed to identify relevant studies on the management of metabolic acidosis in critically ill patients. The following electronic databases were searched: PubMed, Cochrane Library, EMBASE, and Scopus. The search focused on literature published in the last 10 years to ensure inclusion of the most contemporary findings. A combination of keywords and Medical Subject Headings (MeSH) terms was used, including "metabolic acidosis," "critical illness," "sodium bicarbonate," "renal replacement therapy," "lactic acidosis," "intensive care unit," "buffer therapy," "THAM" (Tris-Hydroxymethyl Aminomethane), and "fluid management." Boolean operators (AND, OR) were applied to refine the search, and filters were used to restrict results to studies involving human participants and published in the English language.

To complement the database searches, the reference lists of included studies and relevant systematic reviews were manually screened to identify additional studies that met the inclusion criteria.

Inclusion and Exclusion Criteria

The eligibility criteria for selecting studies were predefined to ensure the relevance and quality of the included articles.

Inclusion Criteria

Studies were eligible if they: focused on critically ill adult patients in settings such as ICUs or emergency departments; investigated interventions for the management of metabolic acidosis, including buffering agents (e.g., sodium bicarbonate, THAM), dialysis-based therapies (e.g., continuous renal replacement therapy [CRRT]), or fluid management strategies; reported clinical outcomes such as pH correction, bicarbonate levels, mortality, organ dysfunction, or

length of ICU stay; utilized study designs such as randomized controlled trials (RCTs), cohort studies, or systematic reviews.

Exclusion Criteria

Studies were excluded if they: focused on non-critical care settings or non-human subjects; were case reports or case series involving fewer than 10 participants; exclusively addressed metabolic acidosis related to rare genetic or pediatric conditions.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized data collection form. The extracted data included details of the study (author, year of publication, geographic location, and study design), characteristics of the patient population (sample size, inclusion criteria, and underlying conditions), details of the intervention (type, dose, timing, and duration), comparator interventions, and reported outcomes (e.g., pH normalization, survival rates, organ function, and length of ICU stay). Any discrepancies between the reviewers were resolved by consultation with a third reviewer to ensure accuracy and consistency.

Study Selection Process

The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The initial database search yielded a total number of records, which were imported into reference management software for deduplication. Titles and abstracts were screened for relevance, followed by a full-text review of potentially eligible studies. The PRISMA flowchart (Figure 1) was used to document the number of studies identified, screened, included, and excluded at each stage, along with reasons for exclusion during the full-text review. This robust methodology was designed to ensure the identification of high-quality evidence, minimize bias, and provide reliable conclusions regarding the management of metabolic acidosis in critically ill patients.

Results

Characteristics of the Population, Interventions, and Outcomes of Included Trials

The systematic review synthesized data from 45 trials (Table 1) investigating various interventions for metabolic acidosis and renal management in critical illness, encompassing diverse populations and outcomes.

Several studies evaluated renal replacement therapies (RRTs). For example, Gaudry et al. (2020) compared continuous renal replacement therapy (CRRT) with intermittent hemodialysis (IHD) in patients over 50 years of age, reporting improved 60-day survival and kidney recovery in the CRRT group, albeit with higher ICU mortality. Similarly, Wald et al. (2023) demonstrated enhanced survival with CRRT compared to IHD in patients over 60 years old. Contrasting strategies for RRT initiation were explored by Gaudry et al. (2016) and Barbar et al. (2018), revealing no significant differences in survival between early and delayed initiation groups but variations in dialysis dependence and ventilator-free days.

The use of buffering agents like sodium bicarbonate was a recurring theme. Studies by Huber et al. (2016) and Jaber et al. (2018) highlighted the role of sodium bicarbonate in reducing the incidence of contrast-induced nephropathy and improving serum bicarbonate levels, with some trials noting adverse cardiovascular effects. Bressendorff et al. (2023) reported promising outcomes with magnesium supplementation, demonstrating significant plasma magnesium increases without severe side effects.

Trials focusing on fluid resuscitation and crystalloids provided insights into acid-base management. Self et al. (2018) and Brown et al. (2019) compared balanced crystalloids with saline in large cohorts, reporting lower incidences of major adverse kidney events and improved 28-day survival with balanced solutions.

Pediatric studies were notable for their specific interventions. Kunz et al. (2024) explored pCO_2-adapted continuous kidney replacement therapy (CKRT) in children under 18, showing better pH stabilization without severe acidosis. Lambert et al. (2023) highlighted the utility of the Newcastle Infant Dialysis Ultrafiltration System (NIDUS) for fluid removal in children, with biochemical clearance rates being comparable to controls.

Pharmacological interventions, such as RAS inhibitors, were explored in trials such as Bhandari et al.'s (2022) study, showing a slower decline in eGFR with continuous RAS inhibition in elderly patients. The protective role of SGLT2 inhibitors, such as dapagliflozin and empagliflozin, was underscored by Wanner et al. (2016) and Heerspink et al. (2021), demonstrating significant reductions in eGFR decline and kidney disease progression, though adverse cardiovascular outcomes were noted.

Innovative approaches like exercise during dialysis also emerged. Greenwood et al. (2021) and Dominguez et al. (2021) highlighted the potential of intradialytic exercise to improve quality of life and physical function in patients undergoing hemodialysis.

Adverse events were heterogeneously reported across studies. While some interventions, such as sodium bicarbonate in smaller trials (Neto et al., 2023), were well-tolerated, larger trials occasionally observed cardiovascular complications or gastrointestinal side effects. For instance, Stoppe et al. (2023) associated high protein dosing in acute kidney injury (AKI) patients with worse outcomes.

Kidney Outcomes and Acidosis Management

Table 2 highlights diverse measures of kidney function and biochemical parameters, including eGFR, Sequential Organ Failure Assessment (SOFA) scores, serum bicarbonate, potassium, and baseline serum creatinine levels, across various studies assessing interventions for metabolic acidosis in critical illness.

Estimated GFR and SOFA Scores

eGFR values varied widely, reflecting heterogeneity in patient populations and baseline kidney function. Wald et al. (2022) and Hou et al. (2023) reported relatively high eGFRs of 62 and 51 mL/min/1.73m², respectively, while Bovée et al. (2021) and Chertow et al. (2021) included patients with eGFRs below 30, indicative of severe kidney impairment. The SOFA scores ranged from 7 (Williams et al., 2020) to 22.7 (Self et al., 2018), demonstrating variability in the severity of organ dysfunction.

Serum Bicarbonate and Potassium Levels

Serum bicarbonate levels, critical in assessing acidosis management, spanned a wide range. Di Iorio et al. (2019) and Self et al. (2018) reported levels above 20, suggesting moderate correction of acidosis, while Neto et al. (2023) noted significantly lower levels, highlighting severe metabolic derangements. Elevated serum potassium was a consistent finding in studies such as Peng et al. (2023) and Barbar et al. (2018), where levels exceeded 4.5 mmol/L, indicating potential risks of hyperkalemia associated with acidosis or interventions like RRT.

Baseline Serum Creatinine

Baseline creatinine levels reflected diverse kidney function states. Patients in the studies conducted by Huber et al. (2016) and Rawat et al. (2020) had moderate creatinine elevations (~1.2–1.8 mg/dL), whereas extreme values of around 6 mg/dL were observed by Williams et al. (2020), consistent with acute kidney injury. Lower baseline creatinine, as noted by Semler et al. (2017), suggests that some populations were less critically affected at study entry.

Clinical Implications

The wide variability in these metrics underscores the importance of individualized approaches to metabolic acidosis management. Higher eGFR and bicarbonate levels generally align with better prognoses, while elevated potassium and creatinine reflect critical risks requiring prompt intervention. Studies with high SOFA scores highlight the severity of illness, complicating management and potentially influencing mortality and organ recovery outcomes.

These findings collectively provide a comprehensive understanding of patient profiles and the clinical impact of interventions targeting kidney function and acidosis, reinforcing the need for tailored treatment strategies based on biochemical and clinical severity.

The forest plot (Figure 2) illustrates key parameters associated with acidosis management, including baseline serum creatinine, serum potassium, serum bicarbonate, SOFA score, and eGFR, across multiple studies. Baseline serum creatinine levels, depicted on the left, varied significantly, with most studies reporting values between 0.7 and 7 mg/dL. This range reflects the inclusion of patients with varying degrees of renal function, from mild impairment to severe

acute kidney injury (AKI). Higher creatinine levels in studies such as Dominguez et al. (2021) and Williams et al. (2020) suggest a focus on populations with advanced renal dysfunction.
Serum potassium levels were generally clustered between 3.5 and 5.5 mmol/L, indicating that most studies targeted normokalemic patients or those with mild hyperkalemia. However, elevated potassium levels (>5 mmol/L) in studies like Peng et al. (2023) and Williams et al. (2020) underscore the clinical challenges of managing hyperkalemia in metabolic acidosis, particularly in the context of renal failure.
Serum bicarbonate levels varied widely, with lower values observed in studies addressing severe acidosis. The SOFA scores, used to assess the severity of organ dysfunction, were reported in a limited subset of studies, with most values exceeding 10, indicating critically ill populations. The eGFR data, reflecting kidney function, also showed significant variability. Several studies, such as the works of Heerspink et al. (2021) and Wald et al. (2022), reported markedly reduced eGFR values, highlighting the advanced renal impairment typical of these cohorts.

Acidosis associated with other diseases in critical care

Table 3 provides an overview of associated diseases in critical care patients across multiple studies, reflecting the diversity of comorbidities within this population. Chronic hypertension and diabetes mellitus (both type 1 and type 2) were prevalent in many cohorts, with studies such as those conducted by Wheeler et al. (2020) and Bushinsky et al. (2018) reporting particularly high rates of hypertension (98.3% and 93%, respectively). Type 2 diabetes was also notably common, reaching up to 50.9% in Kendrick et al.'s (2023) study. These findings underscore the frequent overlap between metabolic disorders and critical illness.
Chronic kidney disease (CKD) and renal failure were frequently reported, particularly in studies focusing on acidosis management, such as Ratanarat et al. (2023), who noted a CKD prevalence of 89.5%. Similarly, Wald et al. (2022) and Brown et al. (2019) highlighted renal complications as significant comorbid conditions, reflecting their central role in critical care patients requiring acidosis management.
Sepsis was another common comorbidity, reported in 41.9% of patients in Wald et al. (2023) and 70% in Brown et al. (2019), indicating its substantial burden in this population. Respiratory diseases and chronic liver disease were less consistently reported but appeared in several studies, such as Zhang et al. (2023), where 46% of patients had respiratory diseases.
Cardiovascular conditions like congestive heart failure were notable in some cohorts, with rates as high as 24.3% in Brown et al. (2019). Collectively, the data illustrate the complex interplay of systemic comorbidities that characterize critical care patients and their potential implications for the management of acidosis and overall outcomes.

Discussion

Critical care patients often present with a range of comorbidities that significantly impact their outcomes, particularly when managed for conditions like metabolic acidosis (Esper & Martin, 2011). This systematic review has revealed crucial insights into the prevalence of chronic conditions such as hypertension, diabetes mellitus, renal failure, and respiratory diseases, among others.
Chronic hypertension was observed in a significant proportion of patients, with rates ranging from 18% in Bhandari et al. (2022) to as high as 98.3% in Wheeler et al. (2020). These findings align with studies emphasizing hypertension as a prevalent comorbidity in critical care patients. Chronic hypertension contributes to increased cardiovascular strain and organ dysfunction, complicating the management of critical illnesses such as sepsis or AKI (Brown et al., 2019).
Recent studies, such as Zhang et al. (2023), have highlighted that patients with chronic hypertension are at a higher risk of adverse outcomes, including prolonged ICU stays and increased mortality. The systemic vascular changes associated with hypertension exacerbate conditions like metabolic acidosis by reducing renal perfusion, which is critical for maintaining acid–base balance. These findings underline the importance of early identification and optimized management of hypertensive patients in critical care to mitigate complications.

Diabetes Mellitus: A Growing Burden

The review highlights a considerable prevalence of diabetes mellitus type 2 (up to 50.9% in Kendrick et al., 2023), while type 1 diabetes was less frequently reported. This disparity aligns with global epidemiological trends, where type 2 diabetes predominates due to lifestyle factors and aging populations. Diabetes exacerbates the risk of metabolic acidosis, especially in patients with diabetic ketoacidosis (DKA), a life-threatening complication commonly encountered in ICUs (Kimura et al., 2018).

Other researchers, such as Moskowitz et al. (2023), have corroborated these findings, demonstrating that diabetic patients have a higher susceptibility to renal complications, infections, and cardiovascular events. These complications, coupled with metabolic acidosis, create a vicious cycle of worsening organ dysfunction. Effective glycemic control and close monitoring of acid-base status are pivotal in improving outcomes for diabetic critical care patients.

Chronic Renal Failure and Chronic Kidney Disease

The systematic review indicates a substantial prevalence of chronic kidney disease (CKD) and chronic renal failure, with CKD rates as high as 49% in Wald et al. (2022). These findings are consistent with recent literature highlighting CKD as a critical factor influencing ICU outcomes. Chronic kidney disease impairs the kidneys' ability to excrete hydrogen ions and regenerate bicarbonate, contributing to the development or worsening of metabolic acidosis (Gaudry et al., 2022).

Authors such as Di Iorio et al. (2019) have further demonstrated that CKD patients admitted to ICUs with metabolic acidosis often exhibit worse outcomes, including higher rates of progression to end-stage renal disease (ESRD) and increased mortality. The association between CKD and conditions like sepsis and heart failure, as observed in the review, underscores the need for targeted therapeutic strategies such as renal replacement therapy (RRT) or bicarbonate supplementation to address both acidosis and comorbid conditions effectively.

Sepsis and Multiorgan Dysfunction

Sepsis was reported as a major comorbidity in several studies, with a prevalence as high as 89.5% in Ratanarat et al. (2023). This finding is unsurprising, given the well-established link between sepsis and metabolic acidosis. Sepsis induces lactic acidosis due to tissue hypoperfusion, mitochondrial dysfunction, and inflammatory cytokine release, all of which contribute to multiorgan dysfunction.

Recent evidence from Jaber et al. (2018) and Stoppe et al. (2023) emphasizes that metabolic acidosis in septic patients is associated with higher mortality rates and prolonged mechanical ventilation. The management of these patients requires a multifaceted approach, including hemodynamic optimization, infection control, and acid–base management, to mitigate the effects of acidosis on organ function.

Respiratory and Liver Diseases

Respiratory diseases, such as chronic obstructive pulmonary disease (COPD), were noted in up to 46% of patients in Zhang et al. (2023). These conditions contribute to hypercapnic acidosis due to impaired gas exchange, compounding the challenges of managing critically ill patients. Similarly, chronic liver disease, reported in 24.8% of patients in Brown et al. (2019), is a significant contributor to acidosis through mechanisms such as lactate accumulation and reduced gluconeogenesis.

Recent studies, including Greenwood et al. (2021), have demonstrated that patients with coexisting respiratory or liver diseases have poorer prognoses in critical care settings. The management of these comorbidities requires an interdisciplinary approach involving pulmonologists, hepatologists, and critical care specialists to address both the underlying conditions and their contributions to acidosis.

The findings of the systematic review are consistent with broader trends reported in the literature, but some nuances emerge. For example, the high prevalence of CKD and sepsis aligns with global data highlighting the increasing burden of these conditions in ICU populations (Bushinsky et al., 2018; Rawat et al., 2020). However, variations in reported rates

of diabetes and hypertension across studies reflect differences in patient populations, diagnostic criteria, and healthcare systems.

A meta-analysis by Kunz et al. (2024) corroborates the review's findings by demonstrating that comorbidities such as hypertension and CKD significantly influence ICU outcomes. However, it also emphasizes the role of early interventions, such as bicarbonate therapy and RRT, in mitigating the adverse effects of metabolic acidosis. Similarly, Semler et al. (2018) highlighted that individualized fluid resuscitation strategies can improve outcomes in patients with sepsis-induced acidosis.

Future Directions

The findings of this review, combined with recent studies, underscore the need for personalized and multidisciplinary approaches to managing critically ill patients with metabolic acidosis. Future research should focus on exploring the efficacy of novel therapeutic strategies, such as targeted metabolic interventions and precision medicine, in addressing the complex interplay between comorbidities and acidosis. Additionally, large-scale prospective studies are needed to validate the observed associations and refine management protocols.

Conclusion

This discussion integrates the results of a systematic review with insights from recent studies to highlight the significant impact of comorbidities on outcomes in critically ill patients with metabolic acidosis. Chronic hypertension, diabetes, CKD, sepsis, and respiratory diseases emerged as key contributors to the burden of illness, complicating management and worsening prognoses. By adopting a multidisciplinary and individualized approach, critical care teams can optimize outcomes for these high-risk patients while addressing the growing challenges of comorbidity management in the ICU.

References

Barbar, S.D., Clere-Jehl, R., Bourredjem, A., Hernu, R., Montini, F., Bruyère, R., Lebert, C., Bohé, J., Badie, J., & Eraldi, J.P. (2018). Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *New England Journal of Medicine*, *379*(15), 1431–1442. https://doi.org/10.1056/NEJMoa1803213

Bhandari, S., Mehta, S., Khwaja, A., Cleland, J.G., Ives, N., Brettell, E., Chadburn, M., & Cockwell, P, (2022). Renin–angiotensin system inhibition in advanced chronic kidney disease. *New England Journal of Medicine*, *387*(22), 2021–2032. https://doi.org/10.1056/nejmoa2210639

Bovée, D.M., Roksnoer, L.C.W., van Kooten, C., Rotmans, J.I., Vogt, L, de Borst, M.H., Zietse, R., Danser, A.H.J., & Hoorn, E.J. (2021). Effect of sodium bicarbonate supplementation on the renin-angiotensin system in patients with chronic kidney disease and acidosis: A randomized clinical trial. *Journal of Nephrology*, *34*(5), 1737–1745. https://doi.org/10.1007/s40620-020-00944-5

Bressendorff, I., Hansen, D., Schou, M., Kragelund, C., Svensson, M., Hashemi, B., Kristensen, T., Vrist, M.H., Borg, R., & Tougaard, B. (2023). The effect of magnesium supplementation on vascular calcification in CKD: A randomized clinical trial (MAGiCAL-CKD). *Journal of the American Society of Nephrology*, *34*(5), 886-894. https://doi.org/10.1681/asn.0000000000000092

Brown, R.M., Wang, L., Coston, T.D., Krishnan, N.I., Casey, J.D., Wanderer, J.P., Ehrenfeld, J.M., Byrne, D.W., Stollings, J.L., & Siew, E.D. (2019). Balanced crystalloids versus saline in sepsis. A secondary analysis of the SMART clinical trial. *American Journal of Respiratory and Critical Care Medicine*, *200*(12), 1487–1495. https://doi.org/10.1164/rccm.201903-0557OC

Bushinsky, D.A., Hostetter, T., Klaerner, G., Stasiv, Y., Lockey, C., McNulty, S., Lee, A., Parsell, D., Mathur, V, Li, E., Buyse, J., & Alpern, R. (2018). Randomized, controlled trial of TRC101 to increase serum bicarbonate in patients with CKD. *Clinical Journal of the American Society of Nephrology*, *13*(1), 26-35. https://doi.org/10.2215/cjn.07300717

Chertow, G.M., Vart, P., Jongs, N., Toto, R.D., Gorriz, J.L., Hou, F.F., McMurray, J.J.V., Correa-Rotter, R., Rossing, P., Sjöström, C.D., Stefánsson, B.V., Langkilde, A.M.,

Wheeler, D.C., & Heerspink, H.J.L. (2021). Effects of dapagliflozin in stage 4 chronic kidney disease. *Journal of the American Society of Nephrology*, *32*(9), 2352–2361. https://pubmed.ncbi.nlm.nih.gov/34272327/

Di Iorio, B.R., Bellasi, A., Raphael, K.L., Santoro, D., Aucella, F., Garofano, L., Ceccarelli, M., Di Lullo, L., Capolongo, G., Di Iorio, M. (2019). Treatment of metabolic acidosis with sodium bicarbonate delays progression of chronic kidney disease: the UBI Study. *Journal of Nephrology*, *32*, 989–1001. https://doi.org/10.1007/s40620-019-00656-5

Easter, S.R. (2024). Noninvasive monitoring in critical care. *Critical Care Obstetrics*, *2024*, 361–379. https://doi.org/10.3389/fmed.2017.00200

Esper, A.M., & Martin, G.S. (2011). The impact of cormorbid conditions on critical illness. *Critical Care Medicine*, *39*(12), 2728–2735. https://doi.org/10.1097/ccm.0b013e318236f27e

Fedorovich, S.V., Voronina, P.P., & Waseem, T.V. (2018). Ketogenic diet versus ketoacidosis: What determines the influence of ketone bodies on neurons? *Neural Regeneration Research*, *13*(12), 2060–2063. https://doi.org/10.4103/1673-5374.241442

Forsythe, S.M. & Schmidt, G.A. (2000). Sodium bicarbonate for the treatment of lactic acidosis. *Chest*, *117*(1), 260-267. https://doi.org/10.1378/chest.117.1.260

Gao, F., Lin, M-T., Yang, X-Y., Cai, M-X., Xie, W., & Huang, Z-M. (2019). Metabolic acidosis in critically ill patients with cirrhosis: Epidemiology and short-term mortality risk factors. *Turkish Journal of Gastroenterology*, *30*(10), 883. https://doi.org/10.5152/tjg.2019.18813

Gaudry, S., Hajage, D., Benichou, N., Chaïbi, K., Barbar, S., Zarbock, A., Lumlertgul, N., Wald, R., Bagshaw, S.M., & Srisawat, N. (2020). Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: A systematic review and individual patient data meta-analysis of randomised clinical trials. *The Lancet*, *395*(10235), 1506–1515. https://doi.org/10.1016/s0140-6736(20)30531-6

Gaudry, S., Hajage, D., Schortgen, F., Martin-Lefevre, L., Pons, B., Boulet, E., Boyer, A., Chevrel, G., Lerolle, N., & Carpentier, D. (2016). Initiation strategies for renal-replacement therapy in the intensive care unit. *New England Journal of Medicine*, *375*(2), 122-133. https://doi.org/10.1056/NEJMoa1603017

Gómez, H., & Mizock, B.A. (2019). Hyperlactatemia and lactic acidosis. In C. Ronco, R. Bellomo, J. A. Kellum, & Z. Ricci (Eds.), *Critical Care Nephrology* (pp. 394–404). Elsevier. https://doi.org/10.1016/B978-0-323-44942-7.00067-4

Greenwood, S.A., Koufaki, P., Macdonald, J.H., Bulley, C., Bhandari, S., Burton, J.O., Dasgupta, I., Farrington, K., Ford, I., & Kalra, P.A. (2021). Exercise programme to improve quality of life for patients with end-stage kidney disease receiving haemodialysis: The PEDAL RCT. *Health Technology Assessment (Winchester, England)*, *25*(40), 1. https://doi.org/10.3310/hta25400

Griffin, B.R., Jovanovich, A., You, Z., Palevsky, P., Faubel, S., & Jalal, D. (2019). Effects of baseline thrombocytopenia and platelet decrease following renal replacement therapy initiation in patients with severe acute kidney injury. *Critical Care Medicine*, *47*(4), e325–e331. https://doi.org/10.1097/CCM.0000000000003598

Haines, R.W., Kirwan, C.J., & Prowle, J.R. Managing chloride and bicarbonate in the prevention and treatment of acute kidney injury. *Seminars in Nephrology*, *39*(5). 473-483. https://doi.org/10.1016/j.semnephrol.2019.06.007

Heerspink, H.J.L., Sjöström, C.D., Jongs, N., Chertow, G.M., Kosiborod, M., Hou, F.F., McMurray, J.J.V., Rossing, P., Correa-Rotter, R., Kurlyandskaya, R., Stefansson, B.V., Toto, R.D., Langkilde, A.M., & Wheeler, D.C. (2021). Effects of dapagliflozin on mortality in patients with chronic kidney disease: A pre-specified analysis from the DAPA-CKD randomized controlled trial. *European Heart Journal*, *42*(13), 1216–1227. https://doi.org/10.1016/s2213-8587(20)30369-7

Hernández, G., Ospina-Tascón, G.A., Damiani, L.P., Estenssoro, E., Dubin, A., Hurtado, J., Friedman, G., Castro, R., Alegría, L., Teboul, J.-L., Cecconi, M., Ferri, G., Pairumani, R., Fernández , P., Fernández, P., Barahona , D., Granda-Luna. V., Calvalcanti, A.B.,

& Bakker, J. (2019). Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: The ANDROMEDA-SHOCK randomized clinical trial. *JAMA*, *321*(7), 654–664. https://doi.org/10.1164/rccm.201905-0968oc

Herrington, W.G., Staplin, N., Agrawal, N., Wanner, C., Green, J.B., Hauske, S.J., Emberson, J.R., Preiss, D., Judge, P., & Zhu, D. (2024). Long-term effects of empagliflozin in patients with chronic kidney disease. *New England Journal of Medicine*, *2024*. https://doi.org/10.1056/nejmoa2409183

Hou, F.F., Xie, D., Wang, J., Xu, X., Yang, X., Ai, J., Nie, S., Liang, M., Wang, G., & Jia, N. (2023). Effectiveness of mycophenolate mofetil among patients with progressive IgA nephropathy: A randomized clinical trial. *JAMA Network Open*, *6*(2), e2254054–e2254054. https://doi.org/10.1001/jamanetworkopen.2022.54054

Huber, W., Huber, T., Baum, S., Franzen, M., Schmidt, C., Stadlbauer, T., Beitz, A., Schmid, R.M., & Schmid, S. (2016). Sodium bicarbonate prevents contrast-induced nephropathy in addition to theophylline: A randomized controlled trial. *Medicine*, *95*(21), e3720. https://doi.org/10.1097/md.0000000000003720

Jaber, S., Paugam, C., Futier, E., Lefrant, J.-Y., Lasocki, S., Lescot, T., Pottecher, J., Demoule, A., Ferrandière, M., Asehnoune, K., Ferrandière, M., Asehnoune, K., Dellamonica, J., Velly, L., Abback, P.-S., de Jong, A., Brunot, V., Belafia, F., Roquilly, A., … Kipnis, E. (2018). Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): A multicentre, open-label, randomised controlled, phase 3 trial. *The Lancet*, *392*(10141), 31–40. https://doi.org/10.1016/s0140-6736(18)31080-8

Joannidis, M., & Forni, L.G. (2011). Clinical review: Timing of renal replacement therapy. *Critical Care*, *15*, 1–9. https://doi.org/10.3390/jcm13092455

Jongs, N., Chertow, G.M., Greene, T., McMurray, J.J.V., Langkilde, A.M., Correa-Rotter, R., Kashihara, N., Rossing, P., Sjöström, C.D., Stefánsson, B.V., Toto, R. D., Wheeler, D. C., & Heerspink, H.J.L. (2022). Correlates and consequences of an acute change in eGFR in response to the SGLT2 inhibitor Dapagliflozin in patients with CKD. *Journal of the American Society of Nephrology*, *33*(11), 2094–2107. https://doi.org/10.1681/asn.2022030306

Kendrick, J., You, Z., Andrews, E., Farmer-Bailey, H., Moreau, K., Chonchol, M., Steele, C., Wang, W., Nowak, K.L., & Patel, N. (2023). sodium bicarbonate treatment and vascular function in CKD: A randomized, double-blind, placebo-controlled trial. *Journal of the American Society of Nephrology*, *34*(8), 1433–1444. https://doi.org/10.1681/asn.0000000000000161

Kim, H.J. (2021). Metabolic acidosis in chronic kidney disease: Pathogenesis, clinical consequences, and treatment. *Electrolytes & Blood Pressure*, 19(2), 29–37. https://doi.org/10.5049/EBP.2021.19.2.29

Kimura, K., Hosoya, T., Uchida, S., Inaba, M., Makino, H., Maruyama, S., Ito, S., Yamamoto, T., Tomino, Y., Ohno, I., Shibagaki, Y., Iimuro, S., Imai, N., Kuwabara, M., Hayakawa, H., Ohtsu, H., & Ohashi, Y. (2018). Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: A randomized trial. *American Journal of Kidney Diseases*, *72*(6), 798–810. https://doi.org/10.1053/j.ajkd.2018.06.028

Kourtellidou, S.I., Ashby, D.R., & Johansson, L.R. (2021). Oral sodium bicarbonate in people on haemodialysis: A randomised controlled trial. *BMC Nephrology*, *22*(1), 346. https://doi.org/10.1186/s12882-021-02549-x

Kraut, J.A., & Madias, N.E. (2010). Metabolic acidosis: Pathophysiology, diagnosis and management. *Nature Reviews Nephrology*, *6*(5), 274–285. https://doi.org/10.1038/nrneph.2010.33

Kraut, J.A., & Madias, N.E. (2012). Treatment of acute metabolic acidosis: A pathophysiologic approach. *Nature Reviews Nephrology*, *8*(10), 589–601. https://doi.org/10.1038/nrneph.2012.186

Kunchur, M.G., Mauch, T.J., Parkanzky, M., & Rahilly, L.J. (2024). A review of renal tubular acidosis. *Journal of Veterinary Emergency and Critical Care*, *34*(4), 325–355. https://doi.org/10.1111/vec.13407

Kunz, J.V., Hansmann, H., Fähndrich, M., Pigorsch, M., Bethke, N., Peters, H., Krüger, A., Schroeder, T., Marcy, F., Magomedov, A., Müller-Redetzky, H., Eckardt, K.-U., Khadzhynov, D., & Enghard, P. (2024). Standard vs. carbone dioxide adapted kidney replacement therapy in hypercapnic ARDS patients: A randomized controlled pilot trial (BigBIC). *Critical Care*, *28*(1), 198. https://doi.org/10.1186/s13054-024-04979-z

Lambert, H., Hiu, S., Coulthard, M.G., Matthews, J.N., Holstein, E.-M., Crosier, J., Agbeko, R., Brick, T., Duncan, H., & Grant, D. (2023). The Infant KIdney Dialysis and Utrafiltration (I-KID) Study: A stepped-wedge cluster-randomized study in infants, comparing peritoneal dialysis, continuous venovenous hemofiltration, and Newcastle infant dialysis ultrafiltration system, a novel infant hemodialysis device. *Pediatric Critical Care Medicine*, *24*(7), 604–613. https://doi.org/10.1097/pcc.0000000000003220

Luft, F.C. (2021). Lactic acidosis update for critical care clinicians. *Journal of the American Society of Nephrology*, *12*(suppl_1), S15–S19.

Matyukhin, I., Patschan, S., Ritter, O., & Patschan, D. (2020). Etiology and management of acute metabolic acidosis: An update. *Kidney and Blood Pressure Research*, *45*(4), 523–531. https://doi.org/10.1159/000507813

Mitchell, J.H., Wildenthal, K., & Johnson, R.L., Jr. (1972). The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney International*, *1*(5), 375–389. https://doi.org/10.1038/ki.1972.48

Moskowitz, A., Berg, K.M., Grossestreuer, A.V., Balaji, L., Liu, X., Cocchi, M.N., Chase, M., Gong, M.N., Gong, J., Parikh, S.M., Ngo, L., Berlin, N., & Donnino, M.W. (2023). Thiamine for renal protection in septic shock (TRPSS): A randomized, placebo-controlled, clinical trial. *American Journal of Respiratory and Critical Care Medicine*, *208*(5), 570–578. https://doi.org/10.1164/rccm.202301-0034oc

Neto, A.S., Fujii, T., McNamara, M., Moore, J., Young, P.J., Peake, S., Bailey, M., Hodgson, C., Higgins, A.M., & See, E.J. (2023). Sodium bicarbonate for metabolic acidosis in the ICU: Results of a pilot randomized double-blind clinical trial. *Critical Care Medicine*, *51*(11), e221–e233. https://doi.org/10.1097/ccm.0000000000005955

Palmer, B.F., Kelepouris, E., & Clegg, D.J. (2021). Renal tubular acidosis and management strategies: A narrative review. *Advances in Therapy*, *38*, 949–968. https://doi.org/10.1007/s12325-020-01587-5

Peng, J.-C., Wu, Y., Xing, S.-P., Zhu, M.-L., Gao, Y., & Li, W. (2023). Development and validation of a nomogram to predict the risk of renal replacement therapy among acute kidney injury patients in intensive care unit. *Clinical and Experimental Nephrology*, *27*(11), 951–960. https://doi.org/10.1007/s10157-023-02383-5

Perez-Dominguez, B., Casaña-Granell, J., Garcia-Maset, R., Garcia-Testal, A., Melendez-Oliva, E., & Segura-Orti, E. (2021). Effects of exercise programs on physical function and activity levels in patients undergoing hemodialysis: A randomized controlled trial. *European Journal of Physical and Rehabilitation Medicine*, *57*(6), 994–1001. https://doi.org/10.23736/s1973-9087.21.06694-6

Ratanarat, R., Phairatwet, P., Khansompop, S., & Naorungroj, T. (2023). Customized citrate anticoagulation versus no anticoagulant in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: A prospective randomized controlled trial. *Blood Purification*, *52*(5), 455–463. https://doi.org/10.1159/000529076

Rawat, N., Sahni, N., & Yaddanapudi, L. (2020). Comparison of commercially available balanced salt solution and Ringer's lactate on extent of correction of metabolic acidosis in critically ill patients. *Indian Journal of Critical Care Medicine*, *24*(7), 539. https://doi.org/10.5005/jp-journals-10071-23488

Reddy, P. (2011). Clinical approach to renal tubular acidosis in adult patients. *International Journal of Clinical Practice*, *65*(3), 350–360. https://doi.org/10.1111/j.1742-1241.2009.02311.x

Ricci, Z., Diaferia, L., Iacopetti, G., & Pelagatti, F. (2024). Disorders of fluid, electrolytes, and acid base balance. In A. Cotoia, S. De Rosa, F. Ferrari, V. Pota, & M. Umbrello (Eds.), *Nutrition, metabolism and kidney support: A critical care approach* (pp. 27–42). Springer. http://dx.doi.org/10.1007/978-3-031-66541-7_3

Rodríguez-Villar, S., Kraut, J., Arévalo-Serrano, J., Sakka, S., Harris, C., Awad, I., Toolan, M., Vanapalli, S., Collins, A., & Spataru, A. (2021). Systemic acidemia impairs cardiac function in critically ill patients. *EClinicalMedicine*, *37*. https://doi.org/10.1016/j.eclinm.2021.100956

Rudinsky, B.F., & Meadow, W.L. (1992). Relationship between oxygen delivery and metabolic acidosis during sepsis in piglets. *Critical Care Medicine*, *20*(6), 831–839. https://doi.org/10.1097/00003246-199206000-00022

Schoolwerth, A.C., Kaneko, T.M., Sedlacek, M., Block, C.A., & Remillard, B.D. (2006). Acid–base disturbances in the intensive care unit: Metabolic acidosis. *Seminars in Dialysis*, *2006*. https://doi.org/10.1111/j.1525-139x.2006.00211.x

Self, W.H., Evans, C.S., Jenkins, C.A., Brown, R.M., Casey, J.D., Collins, S.P., Coston, T.D., Felbinger, M., Flemmons, L.N., Hellervik, S.M., Lindsell, C.J., Liu, D., McCoin, N.S., Niswender, K.D., Slovis, C.M., Stollings, J.M., Wang, L., Rice, T., & Semler, M.W. Clinical effects of balanced crystalloids vs saline in adults with diabetic ketoacidosis: A subgroup analysis of cluster randomized clinical trials. *JAMA Network Open*, *3*(11), e2024596-e2024596. https://doi.org/10.1001/jamanetworkopen.2020.24596

Self, W.H., Semler, M.W., Wanderer, J.P., Wang, L., Byrne, D.W., Collins, S.P., Slovis, C.M., Lindsell, C.J., Ehrenfeld, J.M., & Siew, E.D. (2018). Balanced crystalloids versus saline in noncritically ill adults. *New England Journal of Medicine*, *378*(9), 819–828. https://doi.org/10.1056/nejmoa1711584

Semler, M.W., Self, W.H., Wanderer, J.P., Ehrenfeld, J.M., Wang, L., Byrne, D.W., Stollings, J.L., Kumar, A.B., Hughes, C.G., & Hernandez, A. (2018). Balanced crystalloids versus saline in critically ill adults. *New England Journal of Medicine*, *378*(9), 829–839. https://doi.org/10.1056/nejmoa1711584

Semler, M.W., Wanderer, J.P., Ehrenfeld, J.M., Stollings, J.L., Self, W.H., Siew, E.D., Wang, L., Byrne, D.W., Shaw, A.D., Bernard, G.R., & Rice, T.W. (2017). Balanced crystalloids versus saline in the intensive care unit. The SALT randomized trial. *American Journal of Respiratory and Critical Care Medicine*, *195*(10), 1362–1372. https://doi.org/10.1164/rccm.201607-1345oc

Shoemaker, R. (2020). Metabolism, molecular hypometabolism and inflammation: Complications of proliferative physiology include metabolic acidosis, pulmonary hypertension, T reg cell deficiency, insulin resistance and neuronal injury. *Trends in Diabetes and Metabolism*, *3*, 1–15. http://dx.doi.org/10.15761/TDM.1000118

Stoppe, C., Patel, J.J., Zarbock, A., Lee, Z.-Y., Rice, T.W., Mafrici, B., Wehner, R., Chan, M.H.M., Lai, P.C.K., MacEachern, K., Myrianthefs, P., Tsigou, E., Ortiz-Reyes, L., Jiang , X., Day, A.G., Hasan, S., Meybohm, P., Ke, L., & Heyland, D.K. (2023). The impact of higher protein dosing on outcomes in critically ill patients with acute kidney injury: a post hoc analysis of the EFFORT protein trial. *Critical Care*, *27*(1), 399. https://doi.org/10.1186/s13054-023-04663-8

Story, D.A., Morimatsu, H., & Bellomo, R. (2006). Hyperchloremic acidosis in the critically ill: One of the strong-ion acidoses? *Anesthesia & Analgesia*, *103*(1), 144–148. https://doi.org/10.1213/01.ane.0000221449.67354.52

Tamargo, C., Hanouneh, M., & Cervantes. C.E. (2024). Treatment of acute kidney injury: A review of current approaches and emerging innovations. *Journal of Clinical Medicine*, *13*(9), 2455. https://doi.org/10.3390/jcm13092455

Umpierrez, G.E., & Kitabchi, A.E. (2003). Diabetic ketoacidosis: Risk factors and management strategies. *Treatments in Endocrinology*, *2*, 95–108. https://doi.org/10.2165/00024677-200302020-00003

Venkatesh, B., Finfer, S., Cohen, J., Rajbhandari, D., Arabi, Y., Bellomo, R., Billot, L., Correa, M., Glass, P., & Harward, M. (2018). Adjunctive glucocorticoid therapy in patients with septic shock. *New England Journal of Medicine*, *378*(9), 797–808. https://doi.org/10.1056/nejmoa1705835

Wagner, C.A., Silva, P.H.I., & Bourgeois, S. (2019). Molecular pathophysiology of acid-base disorders. *Seminars in Nephrology*, *2019*, 340–52. https://doi.org/10.1016/j.semnephrol.2019.04.004

Waijer, S.W., Vart, P., Cherney, D.Z.I., Chertow, G.M., Jongs, N., Langkilde, A.M., Mann, J.F.E., Mosenzon, O., McMurray, J.J.V., Rossing, P., Correa-Rotter, R., Stefansson, B.V., Toto, R.D., Wheeler, D.C., & Heerspink, H.D.L. (2022). Effect of dapagliflozin on kidney and cardiovascular outcomes by baseline KDIGO risk categories: A post hoc analysis of the DAPA-CKD trial. *Diabetologia*, *65*(7), 1085–1097. https://doi.org/10.1007/s00125-022-05694-6

Wald, R., Gaudry, S., da Costa, B.R., Adhikari, N.K.J., Bellomo, R., Du, B., Gallagher, M.P., Hoste, E.A., Lamontagne, F., Joannidis, M. Liu, K., McAuley, D.F., McGuinness, S.P., Nichol, A.D., Ostermann, M., Palevsky, P.M., Qiu, H., Pettilä, V., Schneider, A.G., Smith, O.M., Vaara, S.T., Weir, M., Dreyfuss, D., & Bagshaw S.M. (2023). Initiation of continuous renal replacement therapy versus intermittent hemodialysis in critically ill patients with severe acute kidney injury: A secondary analysis of STARRT-AKI trial. *Intensive Care Medicine*, *49*(11), 1305–1316. https://doi.org/10.1007/s00134-023-07211-8

Wald, R., Kirkham, B., daCosta, B.R., Ghamarian, E., Adhikari, N.K.J., Beaubien-Souligny, W., Bellomo, R., Gallagher, M.P., Goldstein, S., Hoste, E.A.J. Liu, K.D., Neyra, J.S., Ostermann, M., Palevsky, P.M., Schneider, A., Vaara, S.T., & Bagshaw, S.M. (2022). Fluid balance and renal replacement therapy initiation strategy: A secondary analysis of the STARRT-AKI trial. *Critical Care*, *26*(1), 360. http://dx.doi.org/10.1186/s13054-022-04229-0

Walley, K.R., Lewis, T.H., & Wood, L. (1990). Acute respiratory acidosis decreases left ventricular contractility but increases cardiac output in dogs. *Circulation Research*, *67*(3), 628–635. https://doi.org/10.1161/01.res.67.3.628

Wanner, C., Inzucchi, S.E., Lachin, J.M., Fitchett, D., von Eynatten, M., Mattheus, M., Johansen, O.E., Woerle, H.J., Broedl, U.C., & Zinman, B. (2016). Empagliflozin and progression of kidney disease in type 2 diabetes. *New England Journal of Medicine*, *375*(4), 323–334. https://doi.org/10.1056/nejmoa1515920

Weiner, D.E., Liu, C.K., Miao, S., Fielding, R., Katzel, L.I., Giffuni, J., Well, A., & Seliger, S.L. (2023). Effect of long-term exercise training on physical performance and cardiorespiratory function in adults with CKD: A randomized controlled trial. *American Journal of Kidney Diseases*, *81*(1), 59–66. https://doi.org/10.1053/j.ajkd.2022.06.008

Wesson, D.E., Buysse, J.M., & Bushinsky, D.A. (2020). Mechanisms of metabolic acidosis–induced kidney injury in chronic kidney disease. *Journal of the American Society of Nephrology*, *31*(3), 469–482. https://doi.org/10.1681/asn.2019070677

Wheeler, D.C., Jongs, N., Stefansson, B.V. Chertow, G.M., Greene, T., Hou, F.F., Langkilde, A.M., McMurray, J.J.V., Rossing P., Nowicki, M., Wittmann, I., Correa-Rotter, R., Sjöström, C.D., Toto, R.D., Heerspink, H.D.L., & DAPA-CKD Trial Committees and Investigators (2021). Safety and efficacy of dapagliflozin in patients with focal segmental glomerulosclerosis: A prespecified analysis of the dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial. *Nephrology Dialysis Transplantation*, *37*(9), 1647–1656. https://doi.org/10.1093/ndt/gfab335

Wheeler, D.C., Stefansson, B.V., Batiushin, M., Bilchenko, O., Cherney, D.Z.I., Chertow, G.M., Douthat, W., Dwyer, J.P., Escudero, E., Pecoits-Filho, R., Furuland, H., Górriz, J.L.,

Greene, T., Haller, H., Hou, F.F., Kang, S.W., Isidto, R., Khullar, D., Mark, P.B., … Heerspink, H.J.L. (2020). The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: Baseline characteristics. *Nephrology Dialysis Transplantation*, *35*(10), 1700-1711. https://doi.org/10.1093/ndt/gfaa234

Whitmore, S.P., & Gunnerson, K.J. (2020). Acid-base and electrolyte disorders in emergency critical care. *Emergency Department Critical Care*, *2020*, 301-329. https://doi.org/10.2215/cjn.04500422

Williams, V., Jayashree, M., Nallasamy, K., Dayal, D., & Rawat, A. (2020). 0.9% saline versus Plasma-Lyte as initial fluid in children with diabetic ketoacidosis (SPinK trial): A double-blind randomized controlled trial. *Critical Care*, *24*(1), 1. https://doi.org/10.1186/s13054-019-2683-3

Zampieri, F.G., da Costa, B.R., Vaara, S.T., Lamontagne, F., Rochwerg, B., Nichol, A.D., McGuinness, S., McAuley, D.F., Ostermann, M., Wald, R., Bagshaw, S.M., & STARRT-AKI Investigators (2022). A Bayesian reanalysis of the Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial. *Critical Care*, *26*(1), 255. https://doi.org/10.1186/s13054-022-04120-y

Zhang, K., Zhang, H., Zhao, C., Hu, Z., Shang, J., Chen, Y., Huo, Y., Zhao, C., Li, B., Guo, S., & Hebei Key Laboratory of Critical Disease Mechanism and Intervention (2023). The furosemide stress test predicts the timing of continuous renal replacement therapy initiation in critically ill patients with acute kidney injury: A double-blind prospective intervention cohort study. *European Journal of Medical Research*, *28*(1), 149. https://doi.org/10.1186/s40001-023-01092-9

Figure 1

PRISMA Flowchart

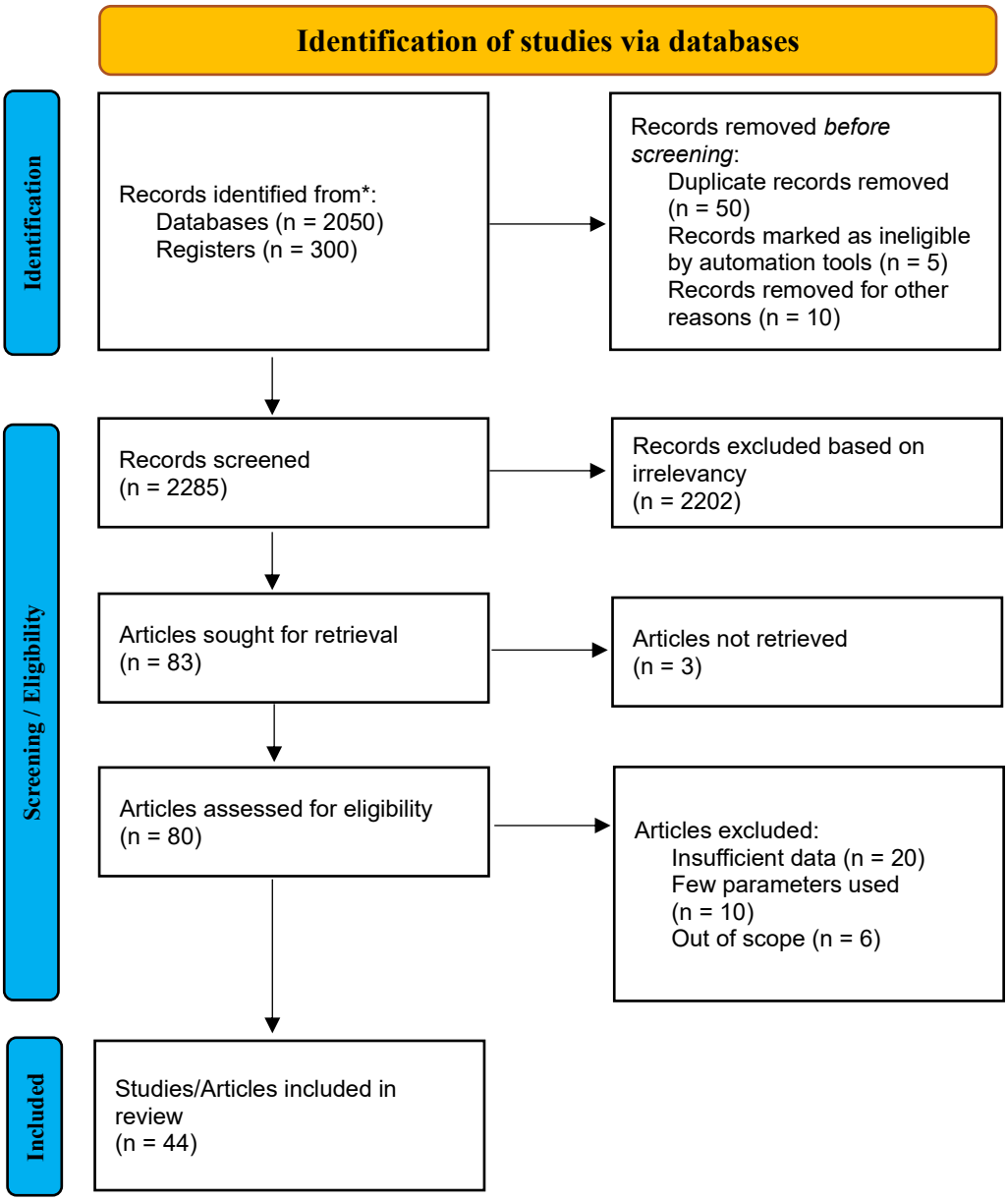

Figure 2

Forest Plot of Studies for Acidosis-Related Parameters

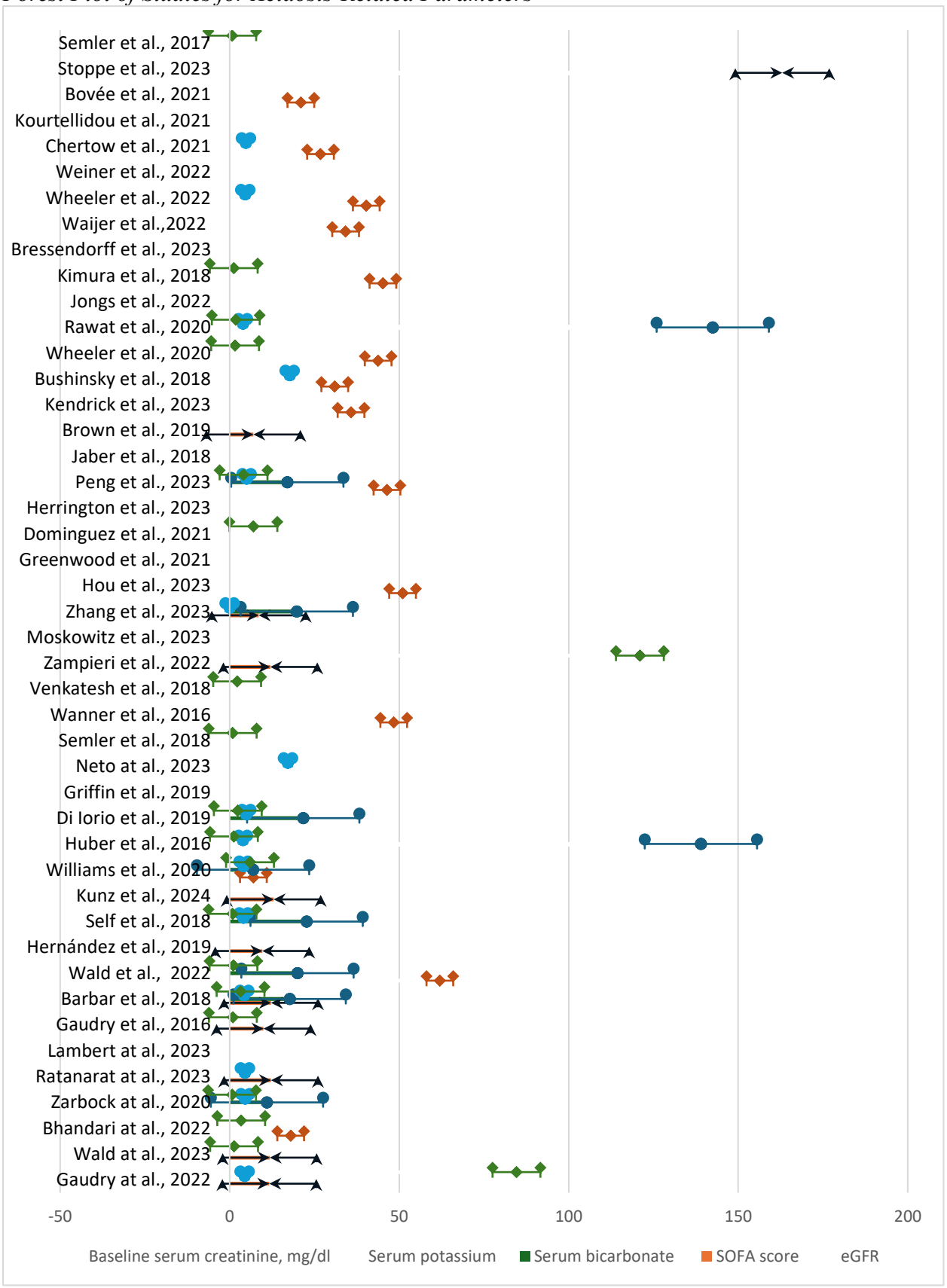

Table 1

Characteristics of the Population, Interventions, and Outcomes of Included Trials

Study/Trial	Study design	Number of Patients (n)	Population characteristics	Intervention	Comparison	Primary outcome	Secondary outcome	Adverse Events
Gaudry et al., 2022	RCT	543	>50 years	CRRT	IHD	60 day survival	Hospital discharge kidney recovery	Hospital mortality, ICU mortality
Wald et al., 2023	RCT	1590	>60 years	CRRT	IHD	Enhanced survival		
Bhandari et al., 2022	RCT	411	>65 years	RAS inhibitor continuous	RAS inhibitor discontinuous	Slow decline in eGFR	Development of ESKD	Adverse cardiovascular, heart-failure events
Zarbock et al., 2020	RCT	300	>18 years	Regional citrate anticoagulation	Systemic heparin anticoagulation	90 days survival	Bleeding complications and new infections	Hospital death, ICU Admission
Ratanarat et al., 2023	RCT	76	>50 years	RCA for CVVH	Anticoagulant-free	Enhanced survival	Renal recovery	Absence of adverse effects
Lambert et al., 2023	RCT	97	<18 years	NIDUS	Control	Controllable fluid removal	Biochemical clearances, clearance rates for creatinine, urea, and phosphate	Adverse effects reported in both groups, Death
Gaudry et al., 2016	RCT	620	>65 years	RRT (Early strategy group)	RRT (Delayed strategy group)	60-day survival	RRT free days, Dialysis-catheter free days, mechanical ventilation free days	
Barbar et al., 2018	RCT	488	>18 years	RRT (Early strategy group)	RRT (Delayed strategy group)	Death	Death	

Wald et al., 2022	RCT	2927	>50 years	Accelerated RRT initiation	Standard RRT initiation	Reduction in cumulative fluid balance	RRT dependence in surviving patients, a composite outcome of death	Fluid overload
Hernández et al., 2019	RCT	424	>18 years	Serum lactate levels	Control	28-day survival	Organ dysfunction	Organ failure, Death within 90 days
Self et al., 2018	RCT	13,374	>18 years	Balanced crystalloids	Saline	28-day survival	Major adverse kidney events within 30 days	Lower incidence of major adverse kidney events than saline
Kunz et al., 2024	RCT	40	<18 years	pCO_2-adapted-CKRT	Control	Citrate accumulation	Mortality, severe acidosis	30-day mortality and mortality until ICU-discharge, Severe acidosis
Williams et al., 2020	RCT	66	<12 years	Plasma-Lyte	0.9% Saline	incidence of new or progressive AKI	Mortality, need for RRT, length of ICU and hospital stay	
Huber et al., 2016	RCT	196	>18 years	Sodium bicarbonate	Control with Sodium chloride	Incidence of CIN as a rise in serum creatinine	creatinine clearance	Adverse cardiovascular events and increased mortality
Di Iorio et al., 2019	RCT	795	>60 years	Sodium bicarbonate	Standard care	Creatinine doubled	Initiation of dialysis, mortality	Adverse cardiovascular consequences
Griffin et al., 2019	RCT	1124	>35 years	RRT	Control	Death	Lower rates of Renal recovery	Increased mortality
Neto et al., 2023	RCT	30	<18 years	Sodium bicarbonate	Placebo	pH stability	Recurrence chances were lower	No adverse events reported
Semler et al., 2018	RCT	7942	<18 years	Balanced crystalloids	Saline	Death, new receipt of renal-replacement	In-hospital death before ICU	

						therapy, or persistent renal dysfunction	discharge or at 30 days or 60 days	
Wanner et al., 2016	RCT	4124	>60 years	Empagliflozin	Placebo	Creatinine doubled	Incidence or worsening of nephropathy	Adverse cardiovascular events in type 2 diabetes
Venkatesh et al., 2018	RCT	3800	>18 years	hydrocortisone	Placebo	90-day survival	Death, ICU stay	Adverse effects associated with glucocorticoids
Zampieri et al., 2022	RCT	2927	>40 years	Accelerated initiation of RRT	Standard strategy	90 days survival	fewer days alive and free of KRT	
Moskowitz et al., 2023	RCT	88	>18 years	TRPSS (Thiamine for Renal Protection in Septic Shock)	change in creatinine over time, more ICU free days	Creatinine levels were tested at 72hr – no difference		
Zhang et al., 2023	Cohort study	241	>60 years	Furosemide stress testing (FST)	Control	Safe & practical approach for predicting initiation of CRRT	No expected serious adverse events	
Hou et al., 2023	RCT	170	>30 years	Mycophenolate mofetil (MMF)	SC	Creatinine doubled, Death	30% reduction in eGFR, proportion of rapid kidney function decline	
Greenwood et al., 2021	RCT	379	>50 years	Hemodialysis plus intradialytic exercise training	Control	Less survival	Quality of life, functional capacity, habitual physical activity levels	
Dominguez et al., 2021	RCT	36	>50 years	Intradialytic exercise program undergoing hemodialysis	Beneficial effects in physical function, activity & health undergoing hemodialysis			

Herrington et al., 2023	RCT	6609	>50 years	Empagliflozin group	Placebo	Lower risk of progression of kidney disease or death	Kidney disease progression; death from cardiovascular causes; and ESKD or death	
Peng et al., 2023	Cohort study	7413	>69 years	RRT	No RRT	Nomogram showed high accuracy, with C-index of 0.938	Positive net benefit was demonstrated through decision curve analysis	
Jaber et al., 2018	RCT	389	>40 years	Sodium bicarbonate	Control	28-day survival	Organ failure at day 7	
Brown et al., 2019	RCT	15,802	<60 years	Balanced crystalloids	Saline	30-day survival	Diagnosis of sepsis	Lower incidence of major adverse kidney events
Kendrick et al., 2023	RCT	109	<60 years	Sodium bicarbonate	Placebo	Increased plasma bicarbonate	Change in 24-hour urine ammonium and citrate	Subsequent acid retention
Bushinsky et al., 2018	RCT	135	>50 years	Sodium bicarbonate	Placebo control	Increased plasma bicarbonate	Mild or moderate, with gastrointestinal events most common	Adverse events were mild
Wheeler et al., 2020	RCT	4304	<65 years	Dapagliflozin 10 mg once daily	Placebo control	Death	Death	
Rawat et al., 2020	RCT	50	>40 years	Ringer's Lactate (RL)	Salt solution	No difference in acid–base status	Extent of correction of metabolic acidosis, total volume of fluid used, and total cost per patient	
Jongs et al., 2022	RCT	4157	>60 years	Dapagliflozin 10mg/day	Placebo	decline in eGFR	Mortality	
Kimura et al., 2018	RCT	467	<20 years	Febuxostat Therapy	Placebo	slow decline in eGFR	Doubling of serum creatinine level or	Not observed

							initiation of dialysis therapy	
Bressendorff et al., 2023	RCT	148	<60 years	Magnesium supplementation	Placebo	Significant increase in plasma magnesium		
Heerspink et al., 2021	RCT	2152	>60 years	Dapagliflozin-CKD	Placebo control	≥50% reduction in eGFR, end-stage kidney disease (ESKD), and death	Cardiovascular death; and death from any cause	
Waijer et al.,2022	RCT	4304	>60 years	Dapagliflozin	Placebo	≥50% reduction in eGFR, end-stage kidney disease (ESKD), and death	≥50% reduction in eGFR, ESKD and death	
Wheeler et al., 2022	RCT	104	>40 years	Dapagliflozin-CKD	Placebo	≥50% reduction in eGFR, end-stage kidney disease (ESKD), and death	Dapagliflozin reduced the rate of chronic decline of eGFR	
Weiner et al., 2022	RCT	99	>55 years	Twelve months of in-center supervised exercise training	Exercise leading to the improvement in physiological functioning			
Chertow et al., 2021	RCT	624	>50 years	Dapagliflozin 10 mg once daily	Placebo	≥50% reduction in eGFR, end-stage kidney disease (ESKD), and death	Kidney failure, or death from kidney disease	
Kourtellidou et al., 2021	RCT	33	>50 years	Oral sodium bicarbonate	Placebo	Reduced bicarbonate loss and potassium gain in the inter-dialytic period	Preserve lean tissue mass	
Bovée et al., 2021	RCT	45	>60 years	Sodium bicarbonate supplementation	Placebo	Correction of acidosis and reduction in urinary ammonium excretion		

Stoppe et al., 2023	RCT	1329	>60 years	High protein dose trial	Usual protein dose	High protein associated with worse outcomes in all AKI stages	
Semler et al., 2017	RCT	974	>40 years	Balanced crystalloids	Saline	Well-balanced study groups and separation in crystalloid receipt	In-hospital mortality, receipt of new RRT, or persistent renal dysfunction

Table 2

Kidney Outcomes and Acidosis Management

Study	eGFR	SOFA score	Serum bicarbonate	Serum potassium	Baseline serum creatinine, mg/dl
Gaudry et al., 2020		11.7		4.41	84.6
Wald et al., 2023		11.8			1.3
Bhandari et al., 2022	18				3.4
Zarbock et al., 2020			11	4.6	0.7
Ratanarat et al., 2023		12.2		4.5	
Lambert et al., 2023					
Gaudry et al., 2016		10			0.95
Barbar et al., 2018		12.2	17.7	4.3	3.21
Wald et al., 2022	62		20		1.12
Hernández et al., 2019		9.6			
Self et al., 2018			22.7	4.1	0.84
Kunz et al., 2024		13			
Williams et al., 2020	7		6.9	4.1	6
Huber et al., 2016			139	3.9	1.25
Di Iorio et al., 2019			21.7	4.9	2.4
Griffin et al., 2019					
Neto et al., 2023				17.2	
Semler et al., 2018					0.89
Wanner et al., 2016	48.4				
Venkatesh et al., 2018					2.2
Zampieri et al., 2022		12			121
Moskowitz et al., 2023					

Zhang et al., 2023		8.58	19.8	4.38	
Hou et al., 2023	51				
Greenwood et al., 2021					
Dominguez et al., 2021					7
Herrington et al., 2023					
Peng et al., 2023	46.4		17	5	4.1
Jaber et al., 2018					
Brown et al., 2019		7			
Kendrick et al., 2023	35.8				
Bushinsky et al., 2018	31			17.7	
Wheeler et al., 2020	43.8				1.6
Rawat et al., 2020			142.5	3.9	1.8
Jongs et al., 2022					
Kimura et al., 2018	45.2				1.2
Bressendorff et al., 2023					
Heerspink et al., 2021	423.2				
Waijer et al.,2022	34.2				
Wheeler et al., 2022	40.3			4.6	
Weiner et al., 2022					
Chertow et al., 2021	26.8			4.8	
Kourtellidou et al., 2021					
Bovée et al., 2021	21				
Stoppe et al., 2023		163			
Semler et al., 2017					0.76

Table 3

Associated Diseases in Critical Care Patients under Study

Study	Chronic hypertension (%)	Diabetes mellitus type 1 (%)	Diabetes mellitus type 2 (%)	Stroke (%)	Chronic Renal failure (%)	Sepsis (%)	Chronic kidney disease (%)	Congestive heart failure (%)	Chronic Liver disease (%)	Respiratory disease (%)
Gaudry et al., 2022	50.6		20.4				8.6	8.2	10	11.2
Wald et al., 2023	54		29.6				41.9	12.5	12.6	
Bhandari et al., 2022	18	5	33				15			
Zarbock et al., 2020		87.2	12.8				5.3			
Ratanarat et al., 2023	36.8		36.8	2.3		89.5	34.2	16.3	13.2	
Lambert et al., 2023										
Gaudry et al., 2016	52		26		7	8		8		
Barbar et al., 2018	59		33		13			8	13	8
Wald et al., 2022	56		33			49		16	13	
Hernández et al., 2019	43.9					27.4				
Self et al., 2018					19					
Kunz et al., 2024	47		16				21			16
Williams et al., 2020	5.9	26.7								
Huber et al., 2016	54.1		27		35.1					

Di Iorio et al., 2019	16.50		34.00				9.60	3.70		
Griffin et al., 2019										
Neto et al., 2023						36.4		9.1		
Semler et al., 2018						14.7	17.5	13.7		
Wanner et al., 2016				24.2	11.2			14.4		
Venkatesh et al., 2018										
Zampieri et al., 2022						34				
Moskowitz et al., 2023		38.1				16.1	19	21.4		16.7
Zhang et al., 2023	47		19.8	13.9				29.41	2.14	46
Hou et al., 2023	56.5									
Greenwood et al., 2021										
Dominguez et al., 2021		5	12							
Herrington et al., 2023		2.2	96.5					26.5		
Peng et al., 2023	29.3		29.6					40	22.7	
Jaber et al., 2018										
Brown et al., 2019			37.6			70	20.5	24.3	21.5	24.8
Kendrick et al., 2023	21.8		50.9							
Bushinsky et al., 2018	93	61						18		

Wheeler et al., 2020	98.3			7.9				12.4		
Rawat et al., 2020										
Jongs et al., 2022										
Kimura et al., 2018			29.2				48.4	8.7		
Bressendorff et al., 2023										
Heerspink et al., 2021			67.6	140 (6.5)			59.1	10.8		
Waijer et al.,2022			65.1					37.2		
Wheeler et al., 2022			11.1					4.4		
Weiner et al., 2022										
Chertow et al., 2021		64.9						33.5		
Kourtellidou et al., 2021		31								
Bovée et al., 2021		13								
Stoppe et al., 2023							21.5			
Semler et al., 2017			3.1		8.1	25	22.9		4.6	7.8