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KIDNEY RESEARCH AND CLINICAL PRACTICE

Unveiling the enigma of acute kidney disease: predicting prognosis, exploring interventions, and embracing a multidisciplinary approach

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Acute kidney disease (AKD) is a critical transitional period between acute kidney injury and chronic kidney disease. The incidence of AKD following acute kidney injury is approximately 33.6%, and it can occur without identifiable preceding acute kidney injury. The development of AKD is associated with increased risks of chronic kidney disease, dialysis, and mortality. Biomarkers and subphenotypes are promising tools to predict prognosis in AKD. The complex clinical situations in patients with AKD necessitate a comprehensive and structured approach, termed "KAMPS" (kidney function check, advocacy, medications, pressure, sick day protocols). We introduce "MAND-MASS," an acronym devised to summarize the reconciliation of medications during episodes of acute illness, as a critical component of the sick day protocols at AKD. A multidisciplinary team care, consisting of nephrologists, pharmacists, dietitians, health educators, and nurses, is an optimal model to achieve the care bundle in KAMPS. Although the evidence for patients with AKD is still lacking, several potential pharmacological agents may improve outcomes, including but not limited to angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptide 1 receptor agonists. In conclusion, accurate prognosis prediction and effective treatment for AKD are critical yet unmet clinical needs. Future studies are urgently needed to improve patient care in this complex and rapidly evolving field.

Keywords: Acute kidney injury, Drug therapy, Patient care team, Prognosis

Introduction

Acute kidney disease (AKD) was first coined in 2012 to describe abnormal kidney function, defined by either serum creatinine level or estimated glomerular filtration rate (eGFR), for less than 3 months [1]. AKD was proposed to identify patients with kidney injury for less than 90 days with or without preceding acute kidney injury (AKI) events (Fig. 1) [2]. AKD can be viewed as a continuum between AKI (kidney injury within 7 days) and chronic kidney disease (CKD, abnormal kidney function or structure beyond 3 months) [1].

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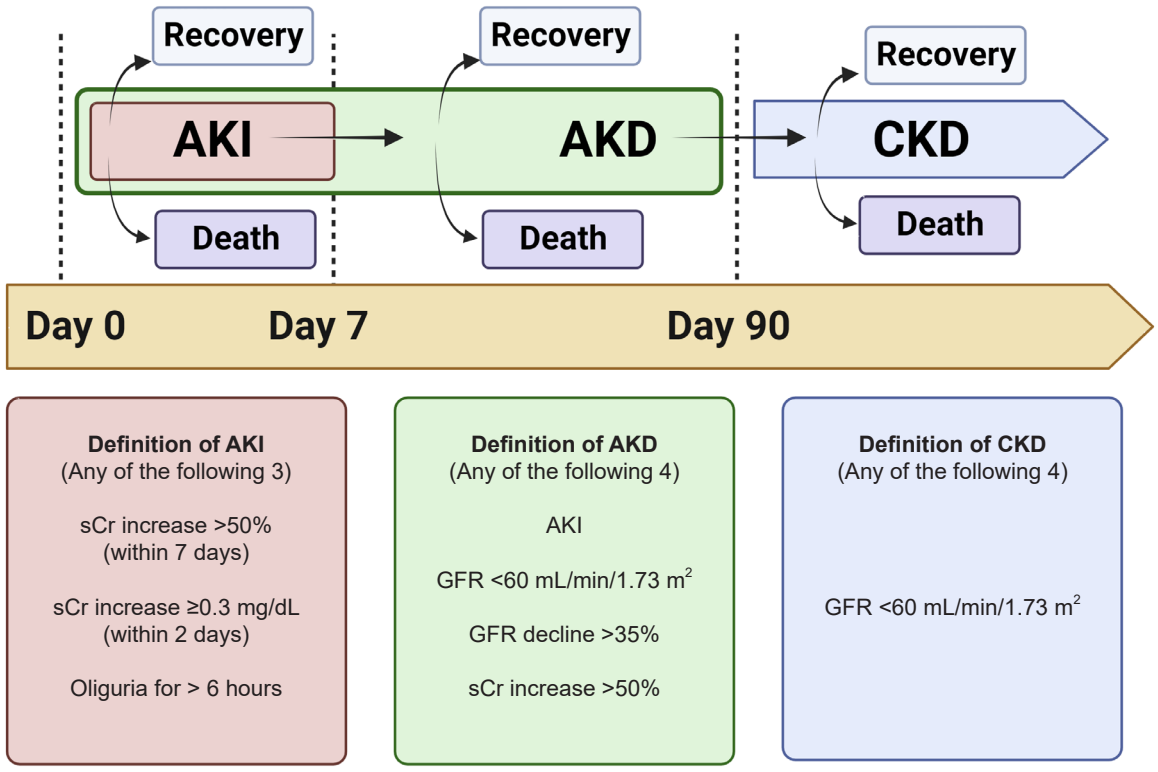

Figure 1. The definition and time frame of AKI, AKD, and CKD. AKI refers to a rapid and abrupt decline in renal function occurring within a period of 2 to 7 days. In contrast, AKD is characterized by the simultaneous presence of kidney damage and abnormal renal function persisting over an extended 90-day timeframe. It's important to note that AKI is encompassed within the broader category of AKD, although AKD can also be defined independently without identification of prior AKI. CKD is defined by persistent kidney function or structural abnormalities lasting for at least 3 months (or 90 days). Markers of structural kidney injury such as albuminuria or hematuria can also be used to define AKD and CKD. Outcomes, such as mortality or the recovery of renal function, may develop across AKI, AKD, and CKD.
AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; sCr, serum creatinine.

A comprehensive systematic review has revealed that, after an episode of AKI, around 33.6% of the patients had AKD [3]. Furthermore, the development of AKD varied significantly across different clinical scenarios, showing a 15.6% incidence in patients with severe malaria-related AKI, 35.9% in patients with postsurgical AKI, and escalating to nearly 40% in patients with myocardial infarction-related AKI [4,5].

It is of paramount importance to highlight that the occurrence of AKD is not solely confined to those with a history of AKI. Specifically, data indicated that the incidence of AKD was 12.3% in hospitalized patients and 4.7% in the general population, irrespective of prior AKI episodes. In line with findings from other investigations, the incidence of AKD in individuals without any previous AKI episodes ranged from 17% to 37.8% [3].

AKI and CKD have been the subject of extensive study, resulting in the formulation of clinical guidelines for patient care [1,6], as expounded in the existing literature. Nevertheless, it is essential to underscore that research concerning AKD remains in its nascent stages. This incipient field confronts several pivotal inquiries that demand further investigation. This review focuses on the intricate domains of AKD prognosis and therapeutic interventions.

Acute kidney disease and clinical outcomes

In patients with AKI or AKD, different outcomes may develop, including death, dialysis, CKD, or recovery of renal function [2]. Studies have consistently reported that AKD is

associated with worse prognosis (mainly subsequent CKD and death) in various disease populations, such as hospitalized patients [7], surgical patients [8], patients with acute decompensated heart failure [9], patients with septic AKI [10], and cirrhotic patients [11]. Importantly, even without identifiable preceding AKI, the prognosis in patients with AKD is still worse than in patients without AKD [3]. This finding justifies the management of AKD as a distinct syndrome other than AKI. Overall, regardless of preceding AKI, the presence of AKD significantly increases the risk of mortality and dialysis [3].

In patients with AKI, the severity of AKI can be staged according to serum creatinine levels [1,12]. A higher AKI stage is associated with poorer outcomes including mortality and dialysis dependence [13–15]. Compared with persistent AKI, early reversal or recovery from an episode of AKI has been consistently associated with better survival [16]. Previous studies have shown that the duration of AKI affects mortality [17]. The longer the duration of AKI, the higher the mortality [17]. In addition, AKD (vs. no kidney disease) was associated with an increased risk of major adverse kidney events (MAKEs), mostly attributed to higher mortality [4].

Acute kidney disease stages

Acute Disease Quality Initiative proposed an AKD staging method, the same as AKI staging, based on changes in serum creatinine levels [18]. Specifically, an AKD stage is defined as stage 0, 1, 2, 3, or dialysis when the ratio of serum creatinine level during AKD over baseline serum creatinine level is <1.5 times increase, 1.5–2.0 times increase, 2.0–3.0 times increase, >3.0 times increase, or under dialysis, respectively. Later, AKD staging based on the eGFR level, the same as CKD staging, was also proposed [2]. Specifically, an AKD stage is defined as 0, 3, 4, 5, or dialysis when eGFR is >60, 30–60, 15–30, <15 mL/min/1.73 m^2, or under dialysis, respectively. Albuminuria may be incorporated into the eGFR-based AKD stages as in the CKD stages.

Several studies have reported a higher serum creatinine-based AKD stage is associated with poorer outcomes [19]. In a retrospective cohort study of 4,741 AKD patients using data from the health information system database of a single tertiary hospital in Taiwan, a higher AKD stage was associated with a higher risk of MAKE (adjusted odds ratio and 95% confidence interval [CI]: AKD stage 1, 1.85 [1.56–2.19]; AKD stage 2, 3.43 [2.85–4.12]; and AKD stage 3, 10.41 [8.68–12.49]; AKD stage 0 as reference) [20].

Novel biomarkers

In AKI, in addition to creatinine-based AKI stages, various novel biomarkers have been reported to predict outcomes [21,22]. These biomarkers include but are not limited to neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid-binding protein (L-FABP), tissue inhibitor of metalloproteinase-2 (TIMP-2), insulin-like growth factor binding protein 7 (IGFBP7), cystatin C, and proenkephalin A (PENK) 119–159. These biomarkers can be categorized as biomarkers of tubular injury (NGAL), tubular function (L-FABP), cell cycle arrest (TIMP-2 and IGFBP7), and GFR (cystatin C and PENK) [21].

The level of urinary L-FABP was also known to predict the need for dialysis, weaning from dialysis, or mortality [23]. TIMP-2 and IGFBP7 are both biomarkers of cell cycle arrest, which play an important role in the pathogenesis of AKI and kidney fibrosis [24]. Urinary [TIMP-2] × [IGFBP7] levels were reported to predict dialysis or death in patients with AKI [25]. Cystatin C, a small protein of about 13 kDa, is produced at a constant rate by nucleated cells, freely filtered by the glomerulus, and nearly completely metabolized in the proximal tubule [26]. The formula incorporating serum cystatin C is reported to better eGFR [27]. The level of serum cystatin C is reported to predict mortality better than serum creatinine [28]. PENK 119–159 was reported to be a predictor of renal recovery after AKI [29].

In patients with AKD, the prognostic value of these biomarkers is less clear. An observational study (French and euRopean Outcome reGistry in ICUs, FROG-ICU) reported that 1-year survival was significantly associated with the levels of biomarkers measured at discharge from the intensive care unit. Among the biomarkers tested in the study (serum creatinine, cystatin C, eGFR, NGAL, and PENK), eGFR estimated by cystatin C had the highest area under the curve for predicting 1-year mortality (0.707; 95% CI, 0.671–0.742) [30]. However, a secondary analysis of the PreCESS (Protocolized Care for Early Septic Shock) trial reported that none of the following five biomarkers—NGAL, L-FABP, [TIMP-2] × [IGFBP7], kidney injury molecule-1, and type 4 collagen—could predict the development of

AKD in patients with septic shock [31]. Recently, AKI subphenotypes have been defined based on a combination of multiple biomarkers and clinical parameters and can be used to predict outcomes in AKI patients [32]. Whether biomarkers or subphenotypes can also be used to predict outcomes in AKD patients remains to be answered.

Potential management

Recent studies have proved several therapeutic interventions to improve outcomes in patients with AKI or CKD. These interventions include AKI bundle care [33], sodium-glucose cotransporter 2 (SGLT2) inhibitor [34], glucagon-like peptide 1 receptor agonist (GLP1-RA) [35], renin-angiotensin-aldosterone system (RAAS) inhibitor [36] including nonsteroidal mineralocorticoid receptor antagonist [37], and very-low-protein diet [38]. However, the evidence of pharmacological intervention in AKD is still accumulating. The proper management of patients with AKD may involve non-pharmacological and pharmacological interventions (Fig. 2). Multidisciplinary care is an important approach in non-pharmacological interventions.

KAMPS

The follow-up and care for patients with AKI or AKD should be guided by the comorbidities of the patients and the severity of the AKI or AKD episode. Based on current expert consensus and limited available literature, we proposed a comprehensive bundle of care for post-AKI or post-AKD management, named "KAMPS" (kidney function check, advocacy, medications, pressure, sick day protocols) [39]. This multifaceted approach integrates a range of strategies such as kidney function tests (including eGFR and albuminuria), meticulous blood pressure control, and a thorough review and adjustment of medications (especially over-the-counter and herbal medicine). Communication is vital in this context, not only among healthcare providers but also with the patient, particularly regarding medications requiring close monitoring during acute illness episodes. This category includes drugs predominantly excreted by the kidneys and nephrotoxic agents, collectively termed "KENDS" (kidney-excreted nephrotoxic drugs) [40]. Regular medication reconciliation and vigilant review are imperative components of AKI or AKD management, necessitating implementation at the initial post-discharge consultation and all subsequent clinic visits. This meticulous approach ensures comprehensive care tailored to individual patient needs, enhancing recovery and minimizing the risk of adverse outcomes.

Sick day protocols and MAND-MASS

In the context of AKD, the establishment of a clearly defined protocol for the resumption of temporarily discontinued medications is imperative. This protocol should be effectively communicated to both the affected individual and their healthcare providers, with meticulous documentation in the individual's medical record to ensure continuity of care.

Figure 2. The four pillars of AKD intervention. These pillars constitute the cornerstone of current, up-to-date therapy for AKD, including angiotensin-converting enzyme inhibitors (ACEi)/ angiotensin receptor blocker (ARB)/mineralocorticoid receptor antagonist (MRA), sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP-1 RA), and multidisciplinary care (MDC). Nonetheless, it's essential to acknowledge that the efficacy of this approach may fluctuate according to individual patient necessities and the particular healthcare context.
AKD, acute kidney disease. Icons were created with www.biorender.com and additional icons were made by Freepik from www.flaticon.com.

The widely endorsed practice of "sick day protocols" for individuals with AKD during episodes of acute, dehydrating illnesses offers specific guidance regarding medication management (Fig. 3). These guidelines typically advise the temporary discontinuation of certain medications in AKD periods during acute illness, including mineralocorticoid receptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, diuretics and direct renin inhibitors, metformin, angiotensin receptor blockers (ARBs), sulfonylureas, and SGLT2 inhibitors [41]. We propose an acronym "MAND-MASS" to summarize important medications to be reconciled during acute illness (Table 1).

Table 1. An acronym designed for reconciling medications in acute illness and a crucial component of sick day protocols

MAND-MASS	
M	Mineralocorticoid receptor antagonists
A	Angiotensin-converting enzyme inhibitors
N	Nonsteroidal anti-inflammatory drugs
D	Diuretics or direct renin inhibitors
M	Metformin
A	Angiotensin receptor blockers
S	Sulfonylureas
S	Sodium-glucose cotransporter 2 inhibitors

However, it is imperative to acknowledge that the existing body of evidence supporting the effectiveness of sick day protocols in preventing the deterioration of kidney function or other clinically significant outcomes in AKD patients remains notably limited. This is a crucial consideration, given the potential harm that may result if individuals encounter challenges in recognizing dehydrating illnesses or determining which medications should be temporarily discontinued.

In situations resulting in dehydration (such as diarrhea, fever, or vomiting) or when the assurance of food intake is compromised (due to nausea, vomiting, or perioperative conditions), certain antidiabetic medications must be temporarily halted [42]. Patients should be informed about the medications that need to be discontinued in these circumstances. Notably, metformin should be temporarily stopped in all situations leading to relevant dehydration, AKI, or hypoxemia due to the risk of lactic acidosis. For diabetic patients with normal baseline renal function on metformin experiencing severe AKI and AKD, the use of metformin should be discontinued when eGFR falls below 30 mL/min/1.73 m^2. Consideration for resuming metformin may be given when renal function recovers later [43].

SGLT-2 inhibitors should be temporarily suspended in situations where carbohydrate intake is compromised

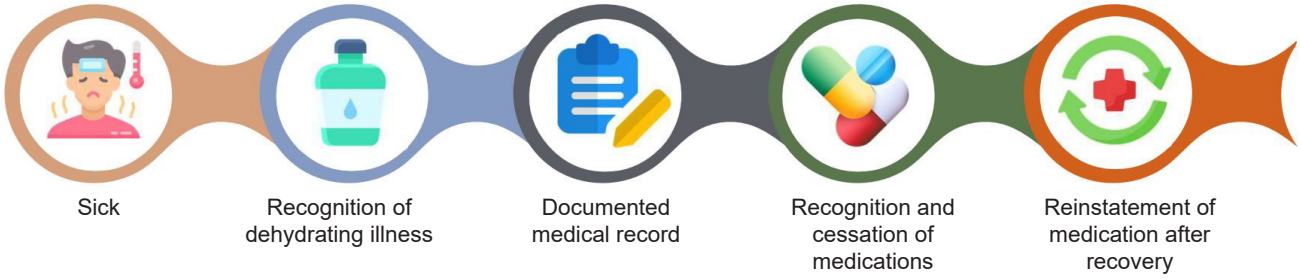

Figure 3. Exploring 'sick day protocols' implementation in acute kidney disease. The sick day protocols comprise several steps. First, identification of sickness. The patient or caregiver should be educated to recognize signs of illness that could lead to further kidney injury, such as vomiting, diarrhea, or fever. Second, identification of dehydration. Dehydration is a common trigger for kidney injury. Patients should be taught to identify signs of dehydration like dry mouth, decreased urine output, and feeling dizzy when standing up. Third, documentation in medical records. All relevant information about the patient's condition and medication should be documented in their medical record. Fourth, identification and stopping of certain medications. Patients should be advised to temporarily stop certain medications when they are sick. These typically include diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs. However, patients must consult with their healthcare provider before stopping any medication. Fifth, recovery and resuming medications. Once the patient has recovered from the illness and their hydration status is back to normal, they can resume their medications as advised by their healthcare provider.
Readers may also refer to Hall RK et al. [41] for the section on "Safe deprescribing." Icons were created by Freepik from www.flaticon.com.

(such as vomiting, prolonged fasting, perioperative settings, or before gastric or colon endoscopy) due to the risk of ketoacidosis [42]. Because SGLT2 inhibitors can cause natriuresis, a drop in blood pressure, and contraction of the glomerular afferent arteriole, theoretically, they might reduce kidney perfusion [44]. Therefore, it is usually recommended to discontinue SGLT2 inhibitors during AKI [45]. However, meta-analyses of large placebo-controlled trials and real-world data revealed that SGLT2 inhibitors decreased the risk of AKI [34,46]. Medications with a propensity for inducing hypoglycemia (e.g., insulin and sulfonylureas) must be temporarily halted or their doses adjusted when carbohydrate intake cannot be guaranteed [42]. Insulin therapy necessitates dose adjustment during acute illness but should never be completely discontinued [47].

Multidisciplinary care

Multidisciplinary team care involves the coordination of care from different disciplines to establish harmonized and structured patient care (Fig. 4). In patients with kidney disease, the multidisciplinary team usually includes nephrologists, pharmacists, dietitians, and health educators. Multidisciplinary team care is a practical model to achieve the bundle care of KAMPS.

The nephrologist bears the critical responsibility of establishing etiological diagnoses and discerning subphenotypes for AKI and AKD. Nephrologists are pivotal in determining which patients are most likely to benefit substantially from post-AKI and post-AKD follow-up care. When considering kidney biopsy to assist diagnosis, judicious selection of appropriate candidates for this invasive intervention is imperative to avoid complications [48]. Elucidating the etiology of AKD is critical in mitigating the recurrence of AKD episodes. Our meta-analysis substantiates that AKI patients receiving post-hospitalization care from nephrologists exhibit a marked reduction in mortality rates compared to those managed by nonspecialists [49]. Beyond the evaluation of etiological factors, the nephrologist's responsibilities extend to orchestrating pertinent follow-up assessments of renal function, determining the necessity and timing of kidney replacement therapy, addressing concurrent medical conditions such as diabetes mellitus, hypertension, and dyslipidemia, and adapting medication regimens according to the prevailing and anticipated course of renal function. The pharmacist plays an important role in the proper dosing of medication based on renal function, avoidance of nephrotoxic agents, and

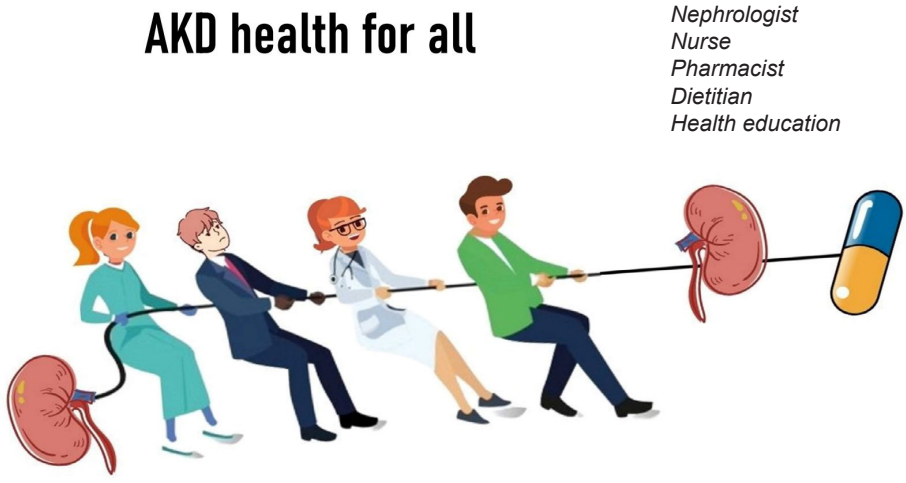

Figure 4. The unfilled gap: multidisciplinary care for preventing deterioration of renal function in AKD. These professionals work together to provide comprehensive care to patients with AKD, aiming to slow the progression of the disease and improve the patient's quality of life. The nephrologist leads the team and provides advanced kidney disease treatment. The pharmacist reconciles medication and educates patients about their prescriptions. The dietitian provides dietary guidance tailored to kidney patients' needs. The health educator or the nurse provides education about lifestyle modifications and self-management strategies to patients. The health educator or the nurse also coordinates patient care with other team members.
AKD, acute kidney disease. Icons were created by Freepik from www.flaticon.com.

evaluation of drug-drug interactions. Frequent assessment of medications in AKD patients is necessary. The dietitian is responsible for the assessment of nutrition status and suggestion of dietary interventions. However, the optimal nutritional therapy in AKI or AKD patients is unclear, especially with dietary protein intake. In a recent trial conducted in the intensive care unit (EFFORT Protein trial), a high-protein diet (≥2.2 g/kg per day) resulted in a higher 60-day mortality rate compared with a normal-protein diet (≤1.2 g/kg per day) in patients with AKI [50]. In line with this finding, a retrospective cohort study reported an association between high protein intake and 60-day mortality in patients cared for at the intensive care unit [51]. Future studies are warranted to investigate the optimal dietary protein intake in AKD patients. Follow-up at a nephrologist clinic during the AKD period may improve outcomes after AKI52. However, even in those who sustained critical illness or dialysis-requiring AKI, only 5.0% to 37.3% of AKD patients received nephrology follow-up after discharge [52,53]. The health educator or the nurse in the multidisciplinary AKD team may mitigate the discrepancy between real-world practice and guideline suggestions by enhancing awareness and knowledge of AKD.

A care bundle based on the Kidney Disease: Improving Global Outcomes (KDIGO) guideline has been shown to improve outcomes in patients with AKI [33], and a randomized controlled trial also showed that multidisciplinary team care reduced albuminuria and hypertension in patients with AKD [54]. A retrospective cohort study, based on data from the Taiwan National Health Insurance Research Database, has revealed that the implementation of multidisciplinary care is linked to a decreased risk of chronic dialysis (hazard ratio [HR], 0.55; 95% CI, 0.49–0.52) as well as a reduced mortality risk (HR, 0.79; 95% CI, 0.57–0.88) among individuals with AKD who have survived an episode of dialysis-requiring AKI [55]. At present, at least three randomized controlled trials are enrolling AKD patients to assess the effectiveness of multidisciplinary team care. These trials are identified as NCT05064904, NCT04145609, and NCT05805709.

Renin-angiotensin-aldosterone system blockade for patients with acute kidney disease

ACE inhibitors and ARBs improve renal outcomes in CKD patients with proteinuria and are recommended as the first-line antihypertensive agent in the guideline [6,56]. A recent study also suggested that there is no need for discontinuation of ACE inhibitors or ARBs in patients with advanced CKD [57]. In the AKD period, several observational studies reported that RAAS inhibitors might be associated with improved survival, increased hyperkalemia, and probably increased risks for kidney adverse events (recurrent AKI and hospitalization due to renal causes) [58].

In addition to ACE inhibitors or ARBs [59], mineralocorticoid receptor antagonists were also reported to decrease the risk of dialysis in AKD patients at the cost of increased risk of hyperkalemia [60]. Recently, finerenone, a nonsteroidal mineralocorticoid receptor antagonist, was reported to improve renal and cardiovascular outcomes in patients with diabetes mellitus and CKD [37]. Notably, compared with traditional mineralocorticoid receptor antagonists, finerenone has a lower risk of hyperkalemia leading to discontinuation of the trial regimen (2.3% or 1.2% on finerenone vs. 0.9% or 0.4% on placebo) [37]. The potential benefits of ACE inhibitors, ARBs, and finerenone in patients with AKD warrant further investigation.

Sodium-glucose cotransporter 2 inhibitor

In patients with CKD or heart failure, SGLT2 inhibitors have been proven to effectively retard the decline of kidney function and reduce the risk of death [34]. These protective effects remain even in non-diabetic patients [34,47]. Furthermore, it provides compelling clinical evidence supporting the associations of SGLT-2 inhibitors in reducing the risk of mortality, and cardiovascular and subsequent kidney disease among patients with type 2 diabetes mellitus and AKD [61]. KDIGO 2023 guideline suggests SGLT2 inhibitors as the first-line drug therapy in diabetic CKD patients with an eGFR of more than 20 mL/min/1.73 m^2 [62].

Currently, at least five trials are testing the effects of SGLT2 inhibitors on the prevention of AKI in patients receiving cardiac surgery (NCT04523064, NCT05852704, and NCT05590143), patients receiving percutaneous coronary intervention (NCT05037695), or patients admitted to the intensive care unit (NCT05468203). Whether SGLT2 inhibitors can accelerate recovery of renal function in patients with AKD is another critical yet unanswered question.

Other potential therapies

GLP-1 RAs constitute an alternative category of therapeutic agents with potential efficacy in managing type 2 diabetes mellitus among patients with AKD. They have exhibited notable cardiovascular benefits in large-scale cardiovascular outcome trials, particularly in the reduction of 3-point major adverse cardiovascular events [63]. Furthermore, GLP-1 RAs confer superior efficacy in terms of lowering A1c levels, reducing lipids, and promoting weight loss, irrespective of the patient's baseline eGFR. Clinical trials investigating the cardiovascular outcomes and glycemic control effects of GLP-1 RAs have encompassed individuals with type 2 diabetes mellitus, both with and without CKD, and eGFR levels as low as 15 mL/min/1.73 m^2 [35].

Moreover, the FLOW study, a complementary and conventional kidney-related outcomes trial (NCT03819153), has been structured to assess the safety and effectiveness of semaglutide in diabetic kidney disease. This randomized, interventional, multicountry study aims to ascertain whether the administration of semaglutide, administered via a weekly subcutaneous injection, in addition to standard care, influences the primary composite endpoint. This endpoint is defined as the persistent decline of eGFR by at least 50% from the trial's initiation, progressing to end-stage kidney disease, death resulting from kidney disease, or cardiovascular-related mortality. Per the trial's protocol, an interim analysis was performed when a predefined number of primary endpoint events had occurred. We eagerly anticipate the release of these results because of early termination [64].

Tirzepatide is a dual-action agent targeting glucose-dependent insulinotropic polypeptide and GLP-1 receptor activation. In an ongoing trial, it also seeks to investigate the impact of tirzepatide on CKD in patients, whether they have type 2 diabetes mellitus or not. The primary outcome measure in this study is the alteration in kidney oxygenation (TREASURE-CKD, NCT05536804).

Several interventions during the AKI period have been reported to improve outcomes, including sodium bicarbonate [65], recombinant human alkaline phosphatase [66], remote ischemic preconditioning [67], acetaminophen [68], levosimendan [69], and atrial natriuretic peptide [70]. Whether the institution of these interventions at the AKD period can improve outcomes warrants further study.

Conclusion

Accurate prognosis prediction and effective treatment remain unmet needs for patients with AKD. It is essential to compare the performance of serum creatinine-based and eGFR-based AKD staging in predicting outcomes. The integration of clinical information and biomarkers for subphenotype identification and outcome prediction holds promise. To address the complexities of clinical scenarios in AKD patients, a multidisciplinary team-based approach is advisable. The collaboration of diverse healthcare professionals with complementary expertise can offer a more holistic and effective approach to patient care, addressing the complexities and nuances of AKD cases comprehensively. Implementing the widely endorsed practice of sick day protocols for individuals with AKD during episodes of acute illness is recommended. Urgent research is warranted to investigate the efficacy and safety of RAAS inhibitors, SGLT2 inhibitors, and potential GLP-1 RAs. The future holds significant promise in the field of AKD, with these research endeavors poised to contribute to enhanced patient outcomes and the advancement of clinical practice.

Conflicts of interest

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Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization, Funding acquisition: SYP, VCW
Formal analysis, Investigation: ZHJ, LCL, IJT, TLW, HCC
Writing–original draft: SYP

Writing–review & editing: VCW, TTMH, CYH, TW, YFL
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