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REVIEW

Acute kidney injury, acute kidney disease and chronic kidney disease: challenges and research perspectives

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ABSTRACT

Acute kidney injury (AKI) and chronic kidney disease (CKD) are interconnected, with AKI often leading to CKD and vice versa. Despite research advances, their causal relationship in clinical settings remains unclear. Inflammation, oxidative stress and maladaptive repair are key factors in AKI's progression to CKD. AKI episodes may hasten CKD progression, influenced by demographics, comorbidities and treatment factors like blood pressure control. This underscores the need for careful management to prevent long-term damage. Prospective cohort studies addressing confounding factors are essential to understanding AKI's impact on CKD. These studies should use precise definitions and measurements to clarify causal pathways and risk factors. Investigating asymptomatic AKI in the general population and CKD patients could offer insights into progression mechanisms and prevention strategies. Understanding the interplay of AKI and CKD is crucial for developing interventions and improving outcomes, making it a scientific and public health priority.

Keywords: AKI, blood pressure, CKD, creatinine, oxidative stress

INTRODUCTION

The concept of acute tubular necrosis, introduced during World War II, marked significant progress in understanding acute renal failure [1]. However, methodological consistency in defining acute renal failure in subsequent studies was lacking, leading to the adoption of various definitions and considerable inconsistency in the literature.

A noteworthy advancement came with the Acute Dialysis Quality Initiative (ADQI), which developed in 2004 the Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease (RIFLE) criteria for diagnosing and classifying a broad range of acute kidney function impairments [2]. This framework introduced the term acute kidney injury (AKI), encompassing both kidney structural damage and dysfunction. The same group later developed the Acute Kidney Injury Network (AKIN) staging system [3]. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines provided a comprehensive framework that unified the RIFLE and AKIN criteria, distinguishing three stages of AKI [4] and subdivisions related to reversibility (Table 1). The ADQI, AKIN and KDIGO guidelines propelled clinical and basic research on AKI. Beginning in 2004, the year of the seminal ADQI paper [2], to December 2024, the annual number of publications registered in PubMed including 'acute kidney injury' or 'acute renal failure' as key terms increased from 1003 to 6057.

THE CONCEPT OF ACUTE KIDNEY DISEASE (AKD)

The 2012 KDIGO AKI guideline group realized that, in practice, some people present with acute (i.e. ≤3 months) kidney function and structural alterations that do not meet the criteria for the definition of either AKI or CKD. An operational definition of AKD was proposed for this group of patients [4]. Some of these patients are asymptomatic and are incidentally found to have elevated serum creatinine, abnormal urine studies (such as proteinuria/albuminuria or microscopic haematuria) or abnormal imaging of the kidneys. These kidney structure or function abnormalities are less severe than in AKI or do not develop as rapidly as in AKI. People with AKD may suffer from the same conditions that cause AKI or CKD and should be identified, evaluated and treated to reverse structural kidney damage before they evolve to AKI or CKD and develop adverse outcomes [5]. Recent data suggest that AKD not associated with AKI is frequent, follows a silent course or is detected late, occurs more frequently in the outpatient

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Table 1: Functional and structural criteria (modified from Lameire *et al.* [5]).

Characteristics	Functional criteria	Structural criteria[a]
Absence of kidney disease	eGFR ≥60 ml/min/1.73 m^2 stable SCr	No damage
AKI	Increase in SCr by 50% within 7 days or increase in SCr by 0.3 mg/dl (26.5 µmol/l) within 2 days or oliguria (urine volume <0.5 ml/min/kg/h) for >6 h	No criteria
AKD	AKI or GFR <60 ml/min/1.73 m^2 for <3 months or a decrease in GFR by ≥35% for <3 months or an increase in SCr by >50% for <3 months	Kidney damage <3 months
CKD	GFR <60 ml/min/1.73 m^2 for >3 months	Kidney damage >3 months

[a]Kidney damage can be assessed by blood or urine markers (proteinuria, abnormal urine sediment, novel biomarkers, imaging or biopsy results).

population and has an overall increased risk of incident and progressive CKD, kidney failure and mortality [6, 7]. In 2017, the ADQI working group proposed a consensus definition of AKD as subacute damage and/or loss of kidney function occurring 7–90 days after AKI as an additional option next to reversible and persistent AKI [8].

DIAGNOSIS AND CLASSIFICATION

The diagnosis and staging classification of AKI/AKD is currently based on serum creatinine (SCr) and/or urine output [9].

SCr is the most widely used surrogate marker to estimate the glomerular filtration rate (GFR), but a large number of conditions affect its non-GFR determinants, including renal functional reserve, muscle metabolism and mass, volume of distribution, hydration status, medications and extrarenal degradation, among others. Therefore, SCr is a delayed and non-specific marker of kidney dysfunction and changes in SCr levels that do not reach KDIGO criteria for AKI may nonetheless represent a loss of function and may take 24–48 h from the point of injury for levels sufficient to define AKI, depending on a patient's muscle mass, hydration status and volume of distribution [10].

Other approaches to evaluating kidney function, including measured GFR, alternative biomarkers like cystatin C and proenkephalin [11] and estimation of 'real-time' or kinetic eGFR, should be considered for diagnosing and staging AKI/AKD.

For example, in prolonged critical illness with a loss of muscle mass and reduced creatinine generation, cystatin C better estimates actual kidney function than plasma creatinine because it is unaffected by muscle loss [12].

However, cystatin C levels are influenced by smoking, inflammation, adiposity, thyroid diseases, malignancy and glucocorticoids, decreasing their value as a measure of renal function [13].

Even if the levels meet AKI criteria, transient SCr increases may reflect potentially reversible haemodynamically driven reductions in GFR, or adequate decongestion in severe cardiac failure patients. Patients who receive adequate, even intensive 'decongestion' have better overall and kidney outcomes than patients in whom diuretics are stopped as soon as the creatinine levels go up. In addition, these changes in SCr are not accompanied by consistent changes in biomarkers of tubular damage [14, 15].

Restoring the volume status with ad libitum water access resulted in the disappearance within 24 h of the genes overexpressed in volume depletion [16].

Also, some drugs may reduce GFR but confer important long-term benefits in retarding the progression of CKD [i.e. angiotensin-converting enzyme inhibitors (ACEis) and sodium–glucose co-transporter 2 inhibitors (SGLT2is)] and the non-steroidal mineralocorticoid receptor antagonist finerenone [17].

EPIDEMIOLOGY

Extensive surveys on AKI incidence and prevalence among hospitalized patients have been conducted worldwide [18]. The reported incidence of AKI among hospitalized people is ≈20% in Europe and North America, with the highest incidence observed in South America at 31%. As mentioned above, AKI is inherently multifactorial, with drug toxicity, sepsis and acute decompensated heart failure as the leading causes [18]. Repeated episodes of AKI, as in patients exposed to cancer chemotherapy, are not rare. The risk of AKI is higher in low- and middle-income countries (LMICs) than in high-income countries (HICs), because contaminated water and endemic and obstetric conditions [19] hugely impact AKI. As health systems in LMICs are often underserved, this results in underreporting and poor outcomes, even if AKI occurs in people with few comorbidities compared with AKI in HICs.

AKI treated in the intensive care unit (ICU) is a well-recognized risk factor for in-hospital mortality, which exhibits a dose–response relationship with AKI stage, with KDIGO stage 3 AKI patients having a death risk seven times higher than those without AKI [20, 21]. A 2017 meta-analysis of 25 studies involving in total of 250 000 hospitalized patients calculated that AKI over a median follow-up of 1.4 years was associated with an 86% increase in cardiovascular death [22]. In this analysis, the relative risk (RR) of cardiovascular conditions was highest for heart failure {RR 1.58 [95% confidence interval (CI) 1.46–1.72]}, followed by acute myocardial infarction [RR 1.40 (95% CI 1.23–1.59)] and stroke [RR 1.15 (95% CI 1.03–1.28)]. Notably, the risk for cardiovascular complications did not differ whether kidney function had evolved towards CKD or not, suggesting that the long-term cardiovascular risk due to AKI is independent of the risk of CKD. Similar results were recently reported by Florens *et al.* [23] in the French Chronic Kidney Disease–Renal Epidemiology and Information Network (CKD-REIN). In contrast, in a 2019 meta-analysis, the risk of AKI evolving to CKD (HR 2.7) [24] was more substantial than that for myocardial infarction and stroke, suggesting that AKI is a significant contributor to the CKD epidemic. Also, a comprehensive review in 2021 emphasized the concern that AKI may have a substantial impact on the CKD epidemic [25].

EXPERIMENTAL MODELS, MALADAPTIVE REPAIR AND RISK FACTORS

The clinical study of AKI presents multiple and complex challenges. Among these difficulties are the heterogeneity of its causes, including transient or persistent renal haemodynamic alterations, infections, exposure to nephrotoxins or a variety of drugs and other inciting events and the time lapse from the injury event until clinical emergence as evidenced by decreased urinary volume and/or a creatinine increase. This is a major obstacle to a comprehensive study of this condition, including the transition from AKI to CKD. Furthermore, most AKI patients are exposed to

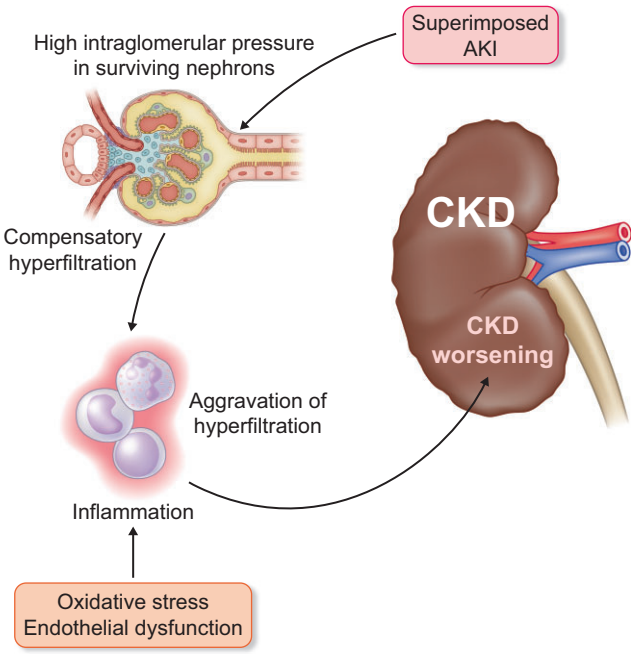

Figure 1: Mechanistic impact of AKI on CKD progression. The issues sketched in this figure are discussed in detail in the main text.

more than one of these pathogenetic mechanisms before and during AKI.

Basic science studies in wild-type and genetically modified animals have shed more light on the long-term relationship between AKI and CKD [26]. In these studies, a fundamental shift in perspective prevails by presenting AKI and CKD as a unified syndrome, independent of the triggering event [27]. In this holistic view, the transition from AKI to CKD is primarily driven by endothelial cell dysfunction [28], inflammation [29] and fibrosis [30], with tubular epithelial cells playing a central role in defining whether the kidneys will recover or dysfunction will progress [31, 32]. Endothelial dysfunction leads to reduced oxygen delivery and subsequent tissue damage, which triggers inflammatory responses. These involve various immune cells, such as macrophages, which play a dual role in injury and repair [29]. Fibrosis, a key feature of CKD, results from inflammation and other mechanisms causing the activation of myofibroblasts to deposit extracellular matrix components, leading to scar formation and impaired kidney function [33]. Injured tubular epithelial cells can undergo polyploidization, where cells increase their DNA content without dividing [34]. This mechanism, along with the proliferation of renal progenitor cells, is crucial for kidney repair and regeneration. However, when repair processes become maladaptive, they can lead to fibrosis and chronic damage, highlighting the delicate balance between regeneration and pathological changes (Fig. 1).

By addressing the underlying mechanisms of maladaptive repair, it may be possible to prevent the progression from acute to chronic organ dysfunction.

In CKD, the kidneys are highly vulnerable to a maladaptive response to injury that is often characterized by altered kidney haemodynamics [35]. The kidneys of CKD patients typically experience increased intraglomerular pressure due to compensatory hyperfiltration in the remaining nephrons [36]. This situation is exacerbated during and after an AKI episode, where the nephrons are further stressed, leading to a vicious cycle of injury and maladaptation. Low eGFR and proteinuria jointly modify the risks of AKI and subsequent adverse clinical outcomes [37]. The compromised autoregulatory capacity in CKD patients means that it is more difficult to maintain a stable kidney blood flow during episodes of AKI, leading to further nephron damage, particularly in case of ischaemia. Inflammation also plays a significant role after AKI in the progression of kidney insufficiency in patients with CKD [38]. The inflammation can result in fibrosis and scarring of the kidney tissue, decreasing the ability to recover after an AKI episode. The persistent inflammatory response can also lead to endothelial dysfunction, contributing to further microvascular damage and impaired healing. Additionally, oxidative stress is pronounced in CKD patients and their kidneys also undergo oxidative stress. Each AKI episode can increase the production of reactive oxygen species, overriding the antioxidant defences. This oxidative stress can damage many cellular components, including lipids, proteins and DNA, leading to apoptosis and necrosis of kidney cells. Moreover, the repair processes in people with CKD are often maladaptive. In contrast with normal repair, a dysregulated repair process frequently leads to fibrosis and further loss of functional nephrons [39]. This maladaptive repair is driven by persistent inflammation, oxidative stress and other factors, leading to progressive kidney damage. Evidence that the occurrence of persistent damage kidney as shown by albuminuria impacts the risk of CKD after an AKI episode has been provided in the well-designed Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) cohort study [40] with a 5-year follow-up.

THE DICHOTOMY BETWEEN NORMAL KIDNEY FUNCTION AND CKD IN eGFR LOSS AFTER AKI: THE CASE OF HYPOTENSION

In the SPRINT trial (NCT01206062), intensive blood pressure (BP) lowering to a systolic BP of <120 mmHg has been shown to reduce cardiovascular events in hypertensive patients at high cardiovascular risk [41]. This approach can lead to acute declines in estimated glomerular filtration rate (eGFR) in 15–20% of these patients, but these declines are considered benign and related to haemodynamic changes rather than to permanent kidney damage [42]. In the same vein, evidence derived from the CORONARY trial (NCT00463294), which enrolled patients undergoing their first isolated coronary artery bypass graft (CABG) surgery, showed that AKI secondary to BP reduction episodes does not impact the long-term risk for CKD in patients with normal or mildly reduced kidney function (average eGFR 75 ml/min/1.73 m^2) [43]. Compared with on-pump surgery, off-pump CABG in this cohort reduced the risk of postoperative AKI by 17%. However, despite this reduction in AKI incidence, there was no significant difference in kidney function at 1 year between the two groups, implying again that AKI in people with normal or quasi-normal kidney function involves no major risk of CKD development.

In contrast, AKI secondary to BP reduction in people with pre-existent CKD does not appear to be a benign condition. Indeed, in a pooled analysis focusing on people with CKD of the Modification of Diet in Renal Disease, African American Study of Kidney Disease, Action to Control Cardiovascular Risk in Diabetes and Systolic Pressure Intervention Trial studies [44] (average eGFR ≈45 ml/min/1.73 m^2), acute declines in eGFR of >15% were more common in patients undergoing intensive BP control than usual BP control and were associated with higher risks of adverse long-term kidney outcomes. Thus, in CKD patients, intensive BP control benefits cardiovascular outcomes, but it may also pose risks for kidney dysfunction with a reduction of eGFR of ≥15%.

CONTRIBUTION OF AKI AND AKD TO THE CKD EPIDEMIC

Jager *et al.* [45] estimated that worldwide in 2017, among patients with kidney diseases (857 million), 844 million individuals had CKD and 13.3 million had AKI. Thus the global CKD burden may be >60 times higher than that of AKI. Detailed estimates of the incidence of AKI/AKD and the risk of the evolution of AKI to CKD have been made in Denmark [46]. This country has a public healthcare system that provides tax-funded general and specialized healthcare to all residents. Since 1968, all Danish residents (≈4.6 million) have been assigned a number in the Danish Civil Registration System at birth or upon immigration, enabling unambiguous information linkage across registries. In the Danish health registry, 169 582 cases of AKI and AKD were registered over 18 years (1990–2018), i.e. 9421 cases/year (2 cases/1000 individuals in the Danish general population). Of the total 169 582 AKI/AKD population, only 20 074 cases (i.e. 11%) developed CKD over the following years. Thus AKI and AKD are rare and rarely evolve into CKD, confirming global estimates made by Jager *et al.* [45]. Overall, the figures from this carefully collected database suggest that AKI and AKD make a minor contribution to the CKD epidemic, even if it is conceivable that some mainly minor AKI cases may not have been registered. The data may not entirely represent countries with a different healthcare system or epidemiology than Denmark.

However, the risk of CKD imposed by AKI may be different in people with and without pre-existing kidney dysfunction. Appropriately designed epidemiology studies and clinical trials still need to better define the link between AKI and the risk of CKD. In the following sections we will discuss the relevance of AKI in patients with established CKD. We then focus on the weaknesses of the observational studies performed so far, eventually pointing to the need for well-designed observational studies and clinical trials.

THE RISK FOR ACCELERATED CKD PROGRESSION BY AKI IN CKD PATIENTS

Although novel drugs substantially reduced the rate of kidney function loss in CKD patients [47], one of today's scenarios hypothesizes that acute insults manifesting as intermittent bouts of either clinical or subclinical AKI rather than linearly progressive renal damage are the main drivers of CKD progression [48].

Over ≈3 years, 42% of CKD patients showed a ≥90% probability of having a non-linear trajectory of kidney function loss [49]. Non-linear eGFR trajectories often underlie rapid decreases in eGFR, followed by a stability period or partial recovery. The non-linear pattern may be useful as an indirect marker of AKI and allows a rather gross estimation of the frequency of AKI/AKD in the course of CKD. In a combined analysis of six trials, Weldegiorgis *et al.* [50] found that among 3523 CKD patients, 26% showed a non-linear eGFR decline across an observation period of ≈3 years, and this pattern was more frequent in diabetic patients (28%) than in non-diabetic patients (9%). In addition, higher baseline eGFR, male sex, steeper eGFR slope and non-renin–angiotensin–aldosterone system antihypertensive therapy were associated with a greater probability of a non-linear eGFR trajectory. More recently, Sikes *et al.* [51], applying KDIGO criteria in 2287 CKD patients in the Salford cohort, estimated the AKI frequency during CKD. A total of 643 (28%) patients suffered one or more AKI events over a median follow-up of 2.6 years, a figure very close to that reported for non-linear evolution of eGFR in the study by Weldegiorgis *et al.* (26%) [50]. Notably, in Sikes *et al.* [51] there was a dose–response relationship between the number of AKI episodes and the risk for kidney failure. Like in the study by Weldegiorgis *et al.* [50], AKI was more frequent among diabetics. Diabetic patients are characterized by afferent arteriolar dilatation, a setting exposing the glomeruli to systemic haemodynamic instability, making them more prone to non-linear eGFR progression [50] and AKI/AKD episodes [52] than non-diabetic patients. In the Salford cohort, smoking and autoimmune or vasculitis-related kidney disease were associated with the risk for AKI. In a separate analysis focusing on fast non-linear CKD progressors [53], these patients had significantly higher rates of mortality.

Table 2: Weaknesses of the most current observational studies testing the hypothesis that the AKI–CKD link is causal.

Problematic aspects	Description
Study design	Predominantly retrospective studies relying on administrative databases, leading to a high likelihood of confounding.
Confounding factors	Age, genetic predisposition, race, ethnicity, socio-economic status, hypertension, diabetes and metabolic syndrome are causal risk factors for AKI and CKD and impact the risk of death and adverse outcomes.
Unaccounted confounders	Severity of pre-existing CKD and other comorbidities not adequately considered. The competing risk for death unaccounted for.
Bias by indication	More severe kidney disease leads to more follow-up eGFR measurements, complicating causal assessment of AKI for CKD.
Data limitations	Inadequate baseline kidney function data can lead to misclassification of AKI and CKD status.
Administrative codes	Dependence on administrative codes for defining AKI and CKD may not capture clinical nuances.
Biomarker collection	Few studies collected specimens for biomarkers to provide precise insights into kidney function and injury.

PROSPECTIVE STUDIES AND CLINICAL TRIALS VERSUS RETROSPECTIVE STUDIES

A major drawback of the available studies that assess the causality of the AKI–CKD link is their predominant retrospective character and reliance on administrative databases with high confounding potential (Table 2). As illustrated in Fig. 2, age, genetic predisposition, race, ethnicity, socio-economic status, hypertension, diabetes and metabolic syndrome predict and are risk factors for both AKI and CKD, but they also impact on the risk of death and adverse cardiovascular and kidney outcomes. A variable is considered a potential confounder for an unfavourable outcome when it associates with both the predictor variable (in this case, age, genetic predisposition and the other factors indicated above) and the outcome (in this case, the risk of death and cardiovascular and kidney disease). Furthermore, retrospective data can introduce confounding factors that are difficult to control. Due to bias by indication, patients with more severe kidney disease have more follow-up eGFR data, while inadequate baseline data on kidney function may lead to potential misclassification of AKI and CKD status [54]. Observational studies frequently depend on ad-

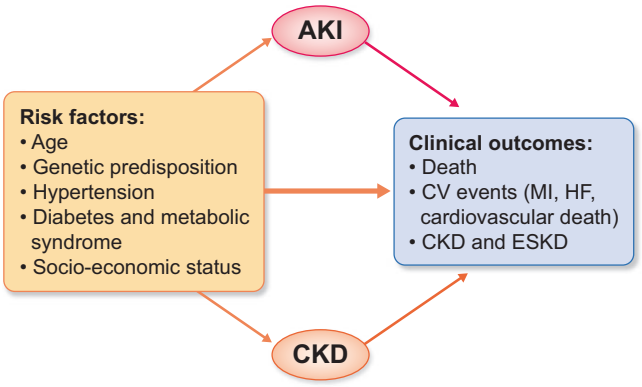

Figure 2: In observational studies, a confounder is a variable associated with both the predictor and the outcome. Age, genetic background, race and ethnicity, hypertension, diabetes and metabolic syndrome are risk factors for AKI and CKD. They also predict relevant kidney outcomes for both conditions and, for this reason, are confounders for interpreting the impact on the risk for CKD and kidney failure of the same conditions.

ministrative codes to define AKI and CKD, which may not accurately capture the clinical nuances of these conditions. Important confounding variables, such as the severity of pre-existing CKD and other comorbidities, may not be adequately accounted for. An important point is that not all observational studies corrected for mortality as a competing outcome. We know from various studies that patients who had AKI in hospital (especially the ICU) have a high 1-year mortality. Unless studies correct for mortality as a competing factor, the relationship with CKD can be masked [55].

The proposed causal relationship between AKI and CKD requires biological plausibility, temporal precedence and strong association [56]. While AKI and CKD share biological plausibility, definitive laboratory evidence is lacking, and the relationship may be bidirectional or indirect. Although AKI often seems to precede CKD in humans, demonstrating a causal link in animal models is challenging. Indeed, ischaemic preconditioning might protect against future injury [57], suggesting that the observed association may not be causal. The scientific evidence for AKI causing CKD in humans is insufficient. A plausible model would involve significant kidney damage followed by recovery and long-term monitoring for signs of CKD. Only well-designed, prospective cohort studies and clinical trials can determine the long-term term impact of AKI on CKD (Fig. 3).

Well-designed prospective cohort studies may minimize confounding by various strategies [58]. The ASSESS-AKI [40] and AKI Risk in Derby (ARID) [59] studies are two examples of how this can be achieved with careful matching of AKI to non-AKI comparator cohorts and timed follow-up study visits. Over a 5-year follow-up period, both studies showed that kidney disease progression occurred in about one-third of those with AKI, even if a high proportion of the enrolled had AKI stage 1, and that albuminuria was present in 42–43%.

The new prospective, multicentre cohort studies assessing the AKI–CKD link should aim to minimize confounding and focus on patients with AKI as defined by KDIGO criteria, with a quarter of patients at AKI stage 2 and a quarter at stage 3. A synchronous cohort of individuals without AKI, well-matched to AKI patients in age, gender, eGFR, cardiovascular disease, diabetes and medical setting, should be included. Previous creatinine levels in non-emergency situations should be collected, along with all other previous laboratory tests, to reconstruct eGFR trends and biochemical evolution before enrolment. The most frequent AKI causes should be adequately represented in the AKI cohort. The study must be powerful enough for sensible preplanned analyses across AKI categories and stages of severity. One of the weaknesses of this approach is the lack of a harmonized screening procedure for kidney function parameters across countries and regions, underscoring the need for advocacy for a well-organized international kidney health screening approach.

Repeated blood and urine collections at prespecified intervals should be conducted to calculate eGFR and assess tubular injury trajectories. Few studies, apart from the ASSESS-AKI and ARID studies, measured biomarkers that could provide more precise insights into kidney function and injury. These limitations hinder the ability to establish a clear causal relationship between AKI and the development of CKD.

A biobank for serum and urine samples and cardiovascular imaging studies should be established. The focus in prospective CKD and non-CKD cohorts should be on the apparent and occult AKI phenotypes, to enable their definition and characterize the risk factors. The collected biological material should also undergo omic analyses.

In almost all observational studies, AKI entails a high cardiovascular risk, particularly for heart failure, which in turn is linked to incident CKD. On biological grounds, an excess risk of severe AKI for these conditions seems likely, but the risk imposed by mild and moderate AKI deserves further study. Episodes of occult AKI are not uncommon among CKD patients with fast progression, and is probably the same among slow and intermediate progressors.

Despite promising results in early-stage research [60], clinical trials for new AKI treatments have not proven effective [39]. These failures may be due to the complex and varied nature of AKI and the intricate underlying causes. Additionally, there may be issues with selecting the right endpoints for the studies, identifying patients likely to develop AKI or determining which patients might benefit from the tested treatments. To tackle these challenges, the 31st ADQI was organized to establish a unified framework for future research [61]. This initiative concentrated on four key areas: strategies for selecting the right patients for studies, research on preventing or reducing the severity of AKI, studies on treatment methods and exploring innovative trial designs beyond the traditional randomized controlled trials.

AN UNEXPLORED PROBLEM: ASYMPTOMATIC, UNDETECTED EPISODES OF AKI/AKD IN THE GENERAL POPULATION

Asymptomatic AKI/AKD episodes in healthy individuals and patients with CKD represent an unexplored research area. High-tech advancements now make AKI/AKD episodes detectable. Creatinine analysers for self-measurement exist [62] and the technology for connecting these instruments to telemedicine systems are available for implementation [63]. Creatinine analysers can be electronically connected to a coordinating centre to allow the results to be stored in a database. The serial creatinine measurements can be used not only for modelling predictive equations, but also for triggering feedback-targeted interventions. Simultaneously, selective urinary collections coinciding with increases in SCr or decreases in eGFR will allow more adequate follow-up of people with kidney dysfunction. This approach can be tested in formal clinical trials, randomizing patients to an intervention arm (feedback arm) or no intervention, i.e. simple registration of the creatinine series. Participants will be instructed

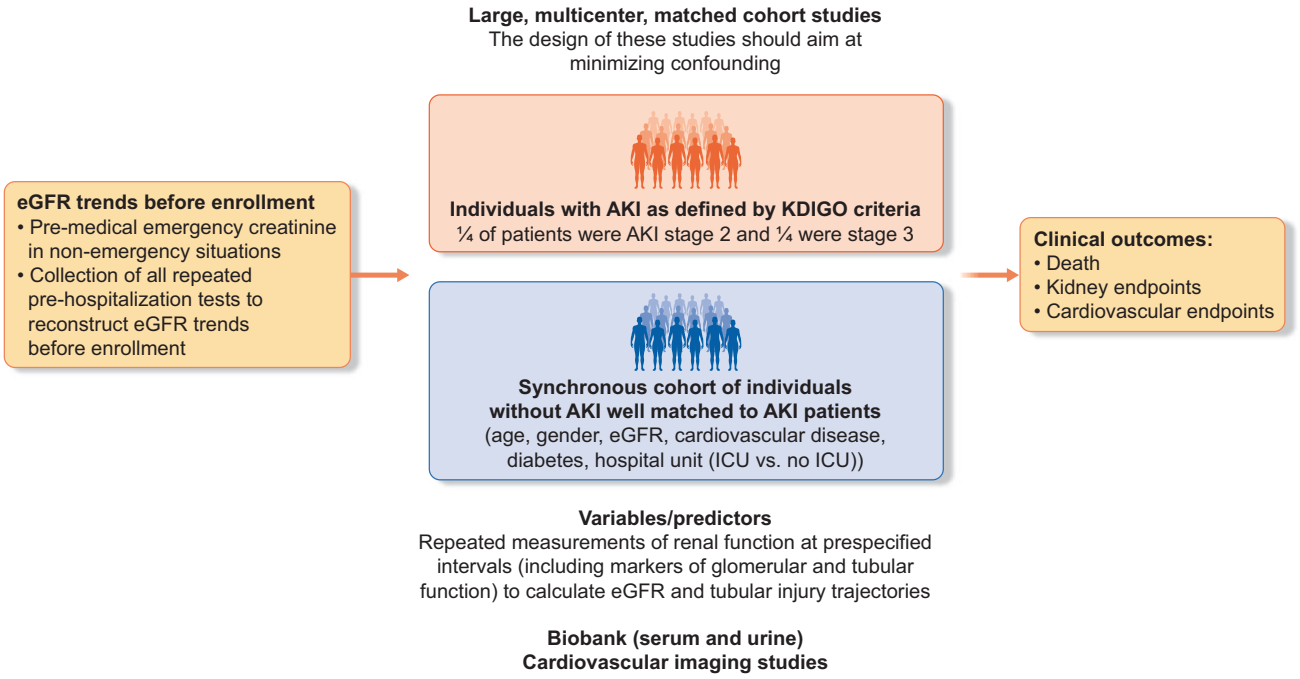

Figure 3: Design of a prospective, matched cohorts study to investigate the link between AKI and CKD.

to collect periodic urine and extra urine on occasions of significant creatinine changes, allowing proteomic and metabolomic studies of the biology of asymptomatic and symptomatic AKI. Because no background information exists on undetected AKI/AKD episodes, preliminary smaller pilot studies are needed to explore the problem in general populations and CKD to allow narrowing of the outline of future large prospective studies. Increases in SCr should be rigorously defined according to the technical variability of SCr in order to eliminate the vagaries due to inherent measurement errors. Specific protocols may be needed for lower-resource settings.

A factor potentially interfering with such analyses is the role of renal functional reserve (RFR) in AKI, which refers to the kidney's ability to increase the GFR in response to physiological stress, such as a protein load or pregnancy. A decrease in RFR suggests a diminished capacity for kidney function compensation, captured by cell cycle arrest biomarkers like tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7, and may predispose to AKI [64]. By the same token, decreased RFR in individuals with normal kidney function, a phenomenon associated with hypertension and diabetes [65], can be at play in asymptomatic, undetected episodes of AKI in the general population. The relationship between RFR and the development of AKI and its transition to CKD deserves attention in future investigations. A possible approach is to perform RFR studies in a random selection of enrolees of AKI studies aimed at describing the relation of RFR with silent, undetected episodes of AKI and their relationship with CKD development.

PERSPECTIVE

The relationship between AKI and CKD remains a significant clinical and research challenge in nephrology. Despite advances in understanding AKI's mechanisms and its potential to accelerate CKD progression, the causal link remains elusive due to methodological limitations in existing observational studies. Prospective cohort studies, with rigorous design and comprehensive data collection, are crucial to unravel this relationship, including those that focus specifically on the period between AKI and day 90, which is crucial for recovery. Addressing confounding factors and ensuring precise definitions and measurements will enhance our understanding of AKI's long-term impact on CKD. Furthermore, the exploration of asymptomatic AKI episodes in both people with CKD and the general population could provide new insights into kidney disease progression and prevention strategies. AKI is a significant risk factor for the development of CKD, particularly when episodes are recurrent or severe and require dialysis treatment. Early detection and management of AKI can prevent progression to CKD. Raising awareness of this problem among primary care providers is fundamental. Thus AKI management should be integrated into medical education, utilizing clinical guidelines and leveraging technology like electronic health record alerts to identify at-risk patients. By enhancing their understanding of AKI, primary care providers can improve patient outcomes and reduce the burden of CKD.

CONCLUSION

The interplay between AKI and CKD is complex and multifactorial, involving biological, clinical and methodological dimensions. Current evidence underscores the need for well-designed prospective studies to clarify the causal pathways and the involved risk factors. By leveraging technological advancements and data collection, future research can address existing gaps, providing a clearer picture of AKI's role in CKD progression. This knowledge is essential for developing targeted interventions and improving patient outcomes. Given the projected increase in CKD prevalence, as well as the increase in AKI provoking events such as heat stress, complex surgery or infections, or in low-resource settings, higher acute survival due to more ade-

quate therapy, understanding and mitigating the impact of AKI is not only a scientific priority but also an important public health priority.

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AUTHORS' CONTRIBUTIONS

C.Z. conceptualized the review and prepared the first draft with R.V. and N.L. C.R., S.F., N.C., N.S., M.O. and F.M. reviewed and edited the draft. C.Z. prepared the final version, which was approved by all authors before submission.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed for this article.

CONFLICT OF INTEREST STATEMENT

C.Z. is a scientific consultant to Fresenius Medical Care Europe and the Middle East and an advisor to Behring. C.R. is an advisor for ASAHI, Baxter, GE, Jafron and Medtronic and has received fees for lectures from Astute, bioMérieux, B. Braun, CytoSorbents, ESTOR, FMC and Toray. N.C. has received honoraria for lectures from AstraZeneca. N.S. holds a grant from Baxter. The remaining authors declare no conflicts of interest.

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