

The global epidemiology of acute kidney injury: challenges and opportunities

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Abstract

Acute kidney injury (AKI) is a devastating complication of acute illness that affects adults and children across multiple settings worldwide and is associated with the development and progression of chronic kidney disease, increased mortality and increased resource utilization. Over the past two decades, standardization of criteria for AKI diagnosis and staging and the publication of multicentre studies have led to improved understanding of the AKI spectrum and provided insights into the heterogeneity of patient characteristics, processes of care and the environmental and sociodemographic factors that influence care delivery and outcomes. Substantial advances have been made in the utilization of electronic health records, biomarkers and care bundles – structured sets of evidence-based treatment practices – to improve the clinical management of AKI. The emerging fields of artificial intelligence and digital health may also provide ways to reduce the burden of this disease. However, these developments have occurred mainly in high-income countries and have yet to improve care delivery or outcomes in low-resource regions. Progress in the development of specific treatments for AKI is limited, and important gaps in knowledge and clinical practice remain, particularly in relation to the 5R framework (risk, recognition, response, renal support and rehabilitation) for managing AKI. An urgent need exists to address the wide variation and inequities in AKI management worldwide.

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Key points

- Acute kidney injury (AKI) is an important global health issue that affects all ages and populations and is associated with serious adverse health outcomes, but it is often poorly recognized and managed.
- The incidence of AKI is increasing worldwide, with the greatest burden in low- and middle-income countries; however, substantial global disparities and inequities exist in access to AKI care.
- The 5R approach — risk, recognition, response, renal support and rehabilitation — provides a framework for recognizing and managing AKI in diverse populations.
- Kidney health advocacy, improved access to care, agnostic determination of AKI, consideration of patient perspectives and concerted efforts to address knowledge and practice gaps have the potential to reduce the risk and improve the management of AKI and acute kidney disease.
- Addressing health inequities; mitigating the effects of climate change on kidney health; utilization of point-of-care tests, electronic medical records, digital health tools and artificial intelligence; and the development of therapeutic approaches offer opportunities to improve care and outcomes in AKI.

Introduction

Acute kidney injury (AKI) is a common and serious disorder that affects all age groups across multiple settings and can occur de novo or complicate other disease states^{1,2}. AKI is associated with adverse outcomes, including increased mortality^{2–6}, progression to chronic kidney disease (CKD), cardiovascular diseases and hypertension, as well as increased resource utilization and healthcare costs^{3,7–9}. Historically, the epidemiology of AKI and its consequences have been poorly understood owing to the lack of a universally accepted definition. Estimates of the incidence of AKI vary widely between 1% and 66% owing to the use of inconsistent definitions and classification criteria that primarily rely on the application of acute dialysis¹⁰. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) expert group published the first international, multidisciplinary, clinical practice guideline for AKI¹¹ based on evidence review and appraisal of the risk, injury, failure, loss, end-stage (RIFLE)¹² and acute kidney injury network (AKIN)¹³ definitions of AKI as an abrupt decrease in kidney function that occurs over 7 days or fewer¹⁴. The KDIGO definition of AKI¹⁴ includes three AKI stages based on absolute or relative changes in serum creatinine (Scr) from a baseline or reference value or a reduction in body-weight-adjusted hourly urine output over intervals of 6–24 h. The guideline has been extensively adopted worldwide, enabling large epidemiological studies of AKI.

In 2013, the global burden of AKI was estimated to be 13.3 million cases, of which 85% were in low-income or lower-middle-income countries^{1,4}. A meta-analysis of studies published in 2004–2012 reported that almost one in five adults and one in three children experienced AKI while hospitalized⁶. The incidence of AKI in low- and middle-income countries (LMICs) is similar to or higher than that in high-income countries (HICs), but AKI mortality is higher in LMICs⁶. In low-income countries (LICs) where AKI usually develops in the community in the setting of dehydration, infections, pregnancy-related

conditions or environmental toxins, the capacity for timely detection and management of AKI is severely limited¹⁵. Over time, AKI can lead to CKD and non-kidney complications, including dysfunction of other organ systems, infection and disability. The resulting prolongation of hospital stays and the need for kidney replacement therapy (KRT) are major drivers of AKI-associated healthcare costs¹⁶.

National, regional and global statistics suggest that AKI affects one in five hospitalized adults and 50–60% of critically ill patients³. However, considerable variation exists in AKI epidemiology, recognition, treatment and follow-up. In this Review, we describe the spectrum and global burden of AKI, discuss the knowledge and practice gaps that must be addressed to improve AKI care and outline a framework for creating a sustainable infrastructure to address this global health issue.

The spectrum of AKI

Despite standardized KDIGO criteria for the definition of AKI, the reported epidemiology varies substantially owing to differences in populations, clinical settings and study methodologies. These factors are further influenced by the underlying susceptibility, exposures and processes of care, which vary across the world. In resource-rich HICs, AKI is usually hospital-acquired and related to drug nephrotoxicity, infections or surgical procedures, whereas in resource-poor LMICs, environmental exposures, tropical diseases and obstetric complications are more common causes¹⁰. Health policies, payment for health services, the availability of electronic health records (EHRs) and access to care further influence the heterogeneity of AKI and its reporting^{15,17}.

Additional variability results from how the KDIGO criteria are implemented. AKI incidence and severity increase when both SCR and urine output criteria are utilized for diagnosis. Studies differ in the measures used to define baseline or reference creatinine values and how they account for missing baseline data. A scoping review on defining AKI using routinely collected laboratory data showed that 33% of studies did not determine baseline SCR and only 20% defined renal function recovery⁷. In a cross-sectional study of over 2 million people in China, the use of expanded KDIGO criteria, including an increase or decrease in serum creatinine by 50% during the hospital stay, increased the detection of AKI from 0.99% to 2.03%¹⁸. The expanded criteria also enable the identification of community-acquired AKI, because many patients are first encountered with elevated SCR concentrations that subsequently decline. Differentiating community-acquired AKI from hospital-acquired AKI has led to improved understanding of the various features, trajectories and outcomes of community-acquired AKI, which might not be recognized, particularly in low-resource settings¹⁷.

Incorporation of the KDIGO AKI definitions and staging into the International Classification of Diseases codes (ICD-9 and ICD-10) has enabled analyses of large administrative datasets across different settings with variable incidences of AKI¹⁹. However, administrative data relying on AKI diagnosis codes often do not correlate with AKI identified by reviewing SCR data for the same population. For example, an analysis of >4 million hospitalizations of US veterans in 2008–2017 found that 21.3% of patients met AKI SCR criteria, but only 13.9% had an AKI diagnosis code¹⁹. The incidence of AKI based on SCR remained stable, while the incidence of AKI based on diagnostic codes increased from 8.6% to 18.7% during the study period.

The availability of EHRs and prediction algorithms enables AKI to be identified in hospitalized patients using electronic alerts¹⁰. An analysis of all cases of AKI in UK adults in the first 4 years following the introduction of a national AKI electronic-alert system in April 2015

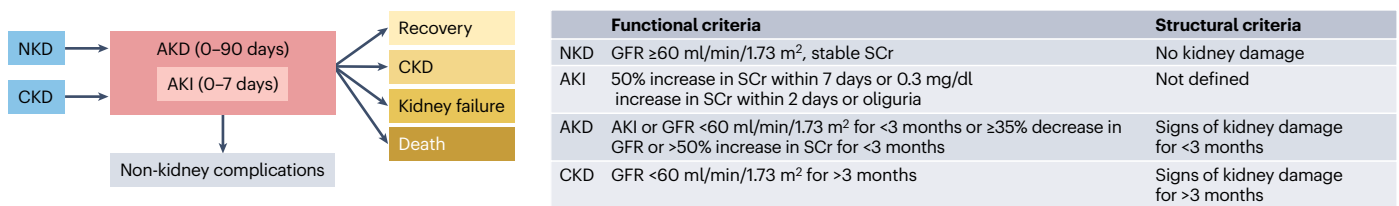


Fig. 1 | KDIGO criteria for kidney disease. Acute kidney disease (AKD) is defined as kidney dysfunction lasting for up to 3 months, bridging the gap between acute kidney injury (AKI), which occurs within 7 days, and chronic kidney disease (CKD), which persists beyond 3 months. AKD represents a continuum in which

incomplete recovery from AKI or new subacute kidney dysfunction can lead either to restoration of function or progression to CKD. AKI and AKD can occur in patients with CKD or no kidney disease (NKD). GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; SCr, serum creatinine.

reported 193,838 episodes in 132,599 patients (the at-risk population is > 10 million)²⁰. The implementation of electronic alerts increased the number of cases of AKI detected and led to an increase in hospitalizations and an improvement in outcomes, which was more pronounced for community-acquired AKI than for hospital-acquired AKI. However, a Scottish study of ICD-10 coding for creatinine-based changes detected by electronic alerts showed poor sensitivity and predictive value for AKI²¹. Although progress is being made in detecting AKI using real-time monitoring, whether these interventions will improve the care and outcomes and/or reduce the burden of AKI is unclear^{22–24}.

AKI, AKD and CKD

AKI, acute kidney disease (AKD) and CKD are increasingly recognized as related entities and in some cases represent a continuum of the disease process²⁵. CKD is defined by the persistence of kidney disease for > 90 days, AKD refers to kidney disease lasting for ≤ 90 days and AKI is defined by a duration of ≤ 7 days^{26,27} (Fig. 1). In a prospective study that included 2,101 patients at community healthcare centres in Bolivia, Malawi and Nepal, 57% had elevated SCr and proteinuria at initial evaluation and no known history of CKD, so they were classified as having AKD^{28,29}. About 30% of the enrolled patients developed AKI within 7 days, of whom $> 40\%$ met the expanded diagnostic criterion of a decline in SCr. The majority of patients who met the expanded criteria for AKI had been classified as having AKD at enrolment. The outcomes of patients with AKD were generally worse than those of patients with no kidney disease. Patients with AKD had an increased likelihood of developing AKI and even those who did not meet AKI criteria had similar mortality to patients with AKI or CKD²⁹.

Population-based studies have shown that patients with AKD who did not fulfil AKI or CKD criteria had comparable outcomes to those with AKI or both CKD and AKI (also known as AKI-on-CKD)³⁰. In four cohorts that included 7 million adults from Canada, Denmark and the UK, the incidences of AKI or AKD ranged from 134.3 to 162.4 per 10,000 patient years and were similar across all regions, with approximately 40% of patients meeting AKD criteria²⁶. A follow-up study of the same cohorts reported similar recovery of kidney function and 1-year mortality among patients with AKD and those with AKI³¹.

The association between AKI and long-term adverse outcomes, including CKD development, has been studied in retrospective studies that are often focused on specific cohorts and lack adequate control groups. In the UK, a prospective, parallel-group, cohort study (AKI Risk in Derby, ARID) confirmed that CKD progression was significantly higher among patients who developed moderate-to-severe forms of AKI during hospitalization (30%) than in a sex- and age-matched group of patients without AKI (7%)³². Recurrent AKI episodes were also more

frequent in the AKI group than the non-AKI group during the 5-year follow-up period.

Application of biomarkers

A major challenge of epidemiological studies in AKI relates to the limitations of SCr. Although widely available and included in current AKI definitions, SCr is not kidney-specific and concentrations are affected by several important comorbid conditions, including sepsis, liver disease, sarcopenia and changes in intravascular fluid status. This limitation influences the diagnosis of AKI and renal recovery^{33,34}.

The availability of kidney-specific biomarkers has enriched understanding of the incidence and mechanisms of AKI^{35,36}. These biomarkers include markers of stress that reflect cell-cycle arrest, markers of tubular damage (with or without dysfunction), and functional biomarkers that correlate with decreased glomerular filtration rate. Application of kidney-specific biomarkers may enable identification of kidney injury at an early stage, before a rise in SCr or decrease in urine output occurs³⁶. This phase of the AKI continuum is often referred to as subclinical AKI³⁷ and is associated with adverse outcomes³⁸. A study that included 178 critically ill children showed that those who had elevated urine neutrophil gelatinase-associated lipocalin (uNGAL) concentrations without a rise in SCr had an almost fourfold increased risk of all-stage AKI on day 3 compared to those without a rise in uNGAL and SCr³⁹. Other studies confirmed an association between subclinical AKI and increased need for KRT and mortality^{40–42}. The Acute Disease Quality Initiative (ADQI) proposed that alternative damage and functional biomarkers should be integrated into the definition and classification of AKI to enable earlier diagnosis of AKI and diagnosis of AKI in the absence of subsequent dysfunction³⁵.

Because patients with AKI are infrequently biopsied, the correlation between SCr concentrations and urinary biomarkers for histologically defined acute tubular injury is unknown⁴³. A cross-sectional analysis of deceased kidney donors who underwent kidney biopsy at the time of organ procurement showed that SCr had poor diagnostic performance in identifying acute tubular injury; 49% of donors with severe acute tubular injury did not meet the SCr criteria for AKI⁴³. The Kidney Precision Medicine Project is an ongoing multicentre prospective cohort study of adults with CKD or AKI who undergo a protocol kidney biopsy for research purposes⁴⁴. The results of this study will enhance our understanding of the AKI disease process and may define molecular pathways for subphenotypes of AKI that are amenable to specific interventions^{45,46}.

The epidemiology of AKI

AKI is a major global contributor to poor patient outcomes^{4,27,47–50} (Fig. 2). The incidence of AKI is increasing worldwide, with the fastest

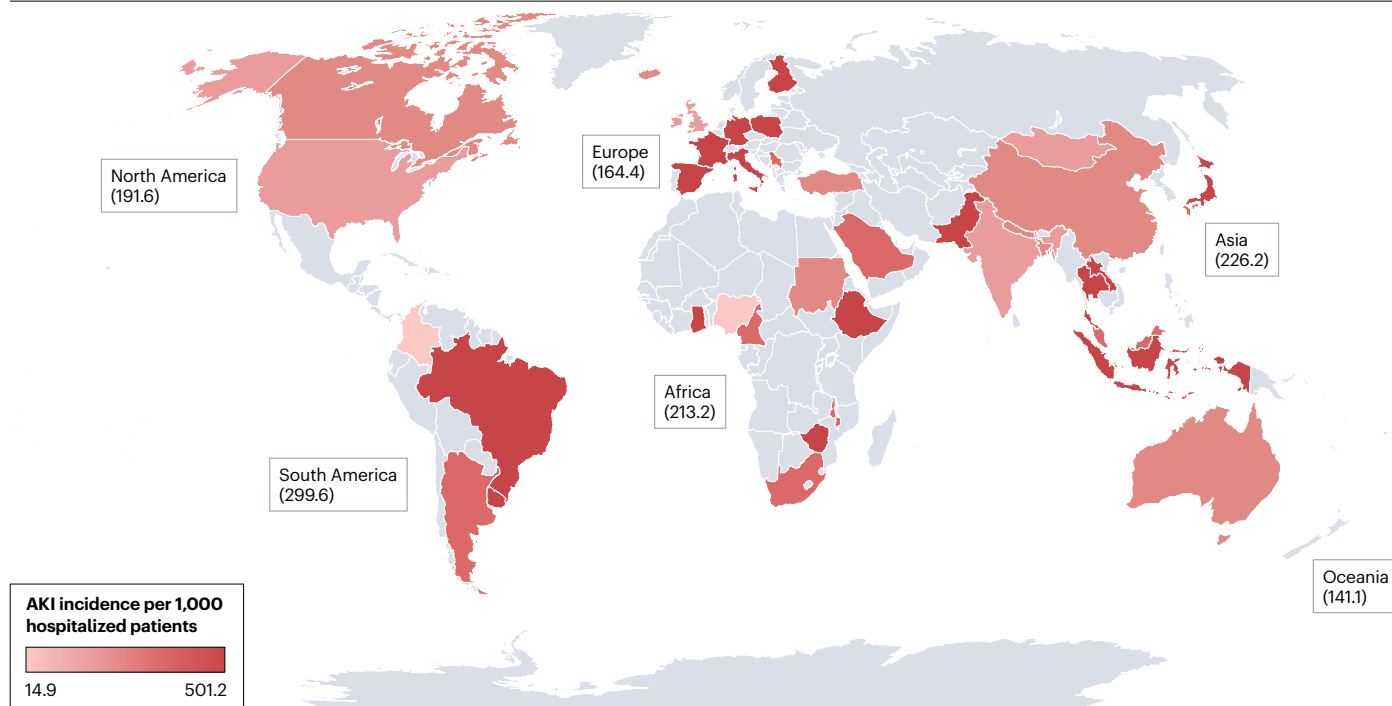


Fig. 2 | The global incidence of AKI. High incidences of acute kidney injury (AKI) are observed in Latin America^{283,284}, Africa^{285–287} and Asia^{48,288–291}, whereas North America, Europe and Oceania^{292–298} report comparatively lower incidences.

The map was constructed by pooling data from a systematic search of studies. Values indicate the region-specific AKI incidence per 1,000 hospitalized patients.

growth in LMICs^{16,47,48}. A meta-analysis of the global burden of AKI (defined using KDIGO-equivalent definitions) that included 154 studies (>3 million patients, primarily in hospital settings) published in 2004–2012 reported pooled AKI incidences of 21.6% in adults (95% confidence interval (CI) 19.3–24.1) and 33.7% in children (95% CI 26.9–41.3), and pooled AKI-associated mortality of 23.9% in adults (95% CI 22.1–25.7) and 13.8% in children (95% CI 8.8–21.0)⁶. AKI-associated mortality declined over the study period and was inversely related to the income of the country and the percentage of gross domestic product spent on total health expenditure. The researchers concluded that 1 in 5 adults and 1 in 3 children worldwide experience AKI during an episode of hospital care. A subsequent analysis in 2015 that included a worldwide sample of 77 million people confirmed that AKI is a major contributor to mortality and poor long-term health^{4,15}.

The prevalence of AKI is higher in critical care settings than in hospital settings and population-based studies⁵¹. The Acute Kidney Injury-Epidemiologic Prospective Investigation (AKI-EPI) study reported that among 1,802 patients who were admitted to intensive care units (ICUs) in 97 centres worldwide, 1,032 (57.3%) had AKI (according to KDIGO criteria) during the first week of ICU admission⁵². AKI severity was positively associated with hospital mortality even after adjustment for other variables, and risk-adjusted rates of AKI and mortality were similar across the world. Patients who developed AKI had worse kidney function at hospital discharge than those without AKI, with an estimated glomerular filtration rate of <60 ml/min/1.73 m² in 47.7% (95% CI 43.6–51.7) versus 14.8% (95% CI 11.9–18.2) of patients, respectively ($P < 0.001$).

In critically ill patients, AKI is usually part of multiorgan failure. However, nonrenal organ failure does not always precede AKI, and

critically ill patients without evidence of organ failure might not be at low risk of AKI⁵³. A study that included 40,152 critically ill patients reported that high-risk patients (those with cardiovascular or respiratory failure in the first 24 hours of ICU admission) had lower survival than low-risk patients (those without cardiovascular or respiratory failure), but the relative increase in mortality that was associated with AKI was greater for low-risk than high-risk patients⁵³. These findings suggest that strategies aimed at preventing AKI should not exclude critically ill patients without cardiovascular or respiratory organ failure.

Biological sex also affects the epidemiology of AKI⁵⁴. Female sex has been associated with a lower incidence of community-acquired AKI, a lower severity of AKI and a lower AKI-associated mortality^{30,55,56}. Genes that escape X-chromosome inactivation, the renoprotective effects of oestrogen, and differences in immune-cell responses or mitochondrial biology have been suggested as possible determinants of sex differences in AKI susceptibility^{54,57–59}.

Paediatric AKI

Critically ill neonates, children and young adults have a high incidence of AKI^{60–63}. A USA study that included 2,644,263 hospitalized children reported that 10,322 (0.39%) developed AKI⁶⁴. The incidence of AKI was highest among teenagers aged 15–18 years (6.6 per 1,000 admissions) and was higher among African American children than among those of other ethnic groups (4.5 versus 3.8 per 1,000 admissions). Identified risk factors suggest that AKI occurs in association with systemic/or multiorgan disease more often than primary renal disease.

In-hospital mortality among patients with AKI was 15.3%, but it was higher among children under a month old (31.3% versus 10.1%,

$P < 0.001$) and children requiring critical care (32.8% versus 9.4%, $P < 0.001$) or dialysis (27.1% versus 14.2%, $P < 0.001$). Shock (odds ratio OR 2.15; 95% CI 1.95–2.36), septicaemia (OR 1.37; 95% CI 1.32–1.43), intubation or mechanical ventilation (OR 1.2; 95% CI 1.16–1.25), circulatory disease (OR 1.47; 95% CI 1.32–1.65), cardiac congenital anomalies (OR 1.2; 95% CI 1.13–1.23) and extracorporeal support (OR 2.58; 95% CI 2.04–3.26) were associated with AKI. Mortality was highest among neonates and children requiring critical care or dialysis.

A secondary analysis of the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study reported that both a single episode of AKI and recurrent AKI were independently associated with longer length of mechanical ventilation, hospitalization, mortality and hypertension at discharge⁶⁵. Neonatal AKI was also independently associated with length of hospital stay.

Although recognition of paediatric AKI has improved, and paediatric AKI is better recognized than adult AKI, important knowledge gaps exist. A more comprehensive understanding of paediatric AKI is required to provide a foundation for future efforts designed to improve outcomes⁶⁰. In particular, paediatric community-acquired AKI, AKI in non-critically-ill children, and cohorts from LMICs have not been well studied⁶¹. An ADQI expert panel suggested that knowledge gaps in paediatric AKI could be addressed by including data from varying socioeconomic groups in AKI studies; individualizing assessment of fluid balance on the basis of underlying organ failure; integrating the biopathology of child growth and development in AKI management; and partnering with families and communities in AKI advocacy initiatives^{28,35,46,66}.

AKI in COVID-19

During the COVID-19 pandemic (February 2020 to May 2023), more than 765 million cases were reported, with nearly seven million deaths worldwide⁶⁷. AKI was a common complication of COVID-19 and a strong risk factor for mortality^{68,69}. Compared to patients with influenza⁷⁰ or other causes of AKI without COVID-19 (ref. 71), those with AKI and COVID-19 had higher mortality, a lower rate of kidney recovery and faster post-discharge decline in estimated glomerular filtration rate. The incidence of COVID-associated AKI ranged from 9.2% to 30.0% in hospitals and from 25.6% to 60.3% in ICUs, depending on the diagnostic criteria, study settings, baseline kidney health status, national income status and phase of the pandemic^{72–77}.

The phenotypes of COVID-associated AKI differed between community and hospital settings. A study that included data from 32,210 patients with COVID-19 in 49 countries reported that the incidence of AKI in the ICU was 53% in LICs, 38% in middle-income countries and 30% in HICs, whereas the rate of dialysis was lower in LICs (27%) than in HICs (45%)⁷⁶. In HICs, the incidence of AKI and dialysis-treated AKI decreased over the course of the pandemic^{69,75,77}. By contrast, a multicentre retrospective study in ten ICUs in Brazil showed that the incidences of AKI and dialysis-treated AKI were higher in the second phase (March to June 2021) than in the first phase (April to August 2020) of the pandemic⁷⁸. Challenges in access to healthcare, limited resources, delayed vaccination and viral variants may have had a role in this difference. In a large international study of 4,158 patients with COVID-19 and kidney disease, kidney health status at hospital admission influenced AKI outcomes⁷⁹. Nearly two-thirds of patients had underlying AKD or CKD at hospital admission and although patients with no kidney disease had the greatest AKI severity, those with AKI superimposed on AKD or CKD had a higher risk of death or non-recovery.

Sepsis-associated AKI

Sepsis is one of the most common causes of AKI in critically ill patients, accounting for 40–50% of cases⁵². Patients with sepsis-associated AKI have a higher risk of death, longer hospital stay, and higher odds of CKD progression than those with AKI without sepsis^{80–82}. Advanced age, organ transplantation, a higher burden of comorbidities, utilization of life-supporting devices and increased illness severity are common risk factors for sepsis-associated AKI^{10,83}. In HICs, the majority of patients with sepsis-associated AKI are admitted to an ICU^{81,84}, whereas in LMICs, patients with sepsis are often cared for in a variety of healthcare settings, depending on the resources available⁸⁵. A systematic review of 47 observational studies published before 25 May 2019 reported that the ICU mortality, hospital mortality and 90-day mortality of patients with sepsis-associated AKI were 46%, 49.8% and 64.7%, respectively⁸⁶. Patients with sepsis-associated AKI and septic shock had the highest mortality. The most prevalent comorbidities were acute respiratory distress syndrome, hypertension and diabetes, but substantial heterogeneity was observed between studies^{59,81,84,85,87}.

Cancer-associated AKI

AKI is a common complication among patients with cancer that often leads to longer hospital stays, modification or discontinuation of cancer treatment, increased risk of chemotherapy-related toxicities and poor prognosis^{88,89}. A population-based study in Denmark reported that the risk of developing AKI (using RIFLE criteria) was 17.5% during the first year and up to 27% during the first five years after a cancer diagnosis⁹⁰. A study of patients initiating systemic cancer therapy in Ontario, Canada, reported a cumulative incidence of AKI (over 8 years) of 9.3%⁹¹. Similarly, a Chinese study reported an AKI incidence of 7.5% among adult patients with cancer⁹².

The incidence of severe AKI (defined as KDIGO AKI stage II or III and need for nephrology in-hospital follow-up) among 315,932 patients with cancer who were admitted to a single tertiary referral oncological centre in Portugal was 1% ($n = 3,201$)⁹³. In this study, 75.7% of patients with severe AKI had solid tumours; gastrointestinal (30.9%), urological (23.6%), and gynaecological (18.1%) tumours were the most prevalent, whereas breast (7.1%), head and neck (5.3%), and lung cancer (5.1%), sarcoma (4.7%) and other solid neoplasms (5.2%) were less common. Non-Hodgkin lymphoma was the most common haematological cancer (29.5%) among patients with severe AKI, followed by multiple myeloma (23.6%), acute myeloid leukaemia (17.0%) and acute lymphoid leukaemia (13.7%).

Haemodynamic instability, obstruction, sepsis and drug-induced nephrotoxicity are often associated with AKI in patients with cancer^{93,94}. Rarer causes of severe AKI include myeloma cast nephropathy, haematopoietic stem cell transplantation, hypercalcaemia, tumour lysis syndrome, thrombotic microangiopathy, leukaemic or lymphomatous infiltration and paraneoplastic glomerulonephritis. Anorexia, nausea, diarrhoea and nephrotoxic medications are common contributing factors. Genito-urinary cancer or extrinsic compression of the urinary tract is the most common cause of ureteral obstruction⁹⁵. Intratubular obstruction may occur secondary to the precipitation of crystals or casts (composed of uric acid, light chains or methotrexate). There is an extensive relationship between cancer drugs and development of kidney pathology^{89,96–104}. Depending on the aetiology, AKI may be accompanied by proteinuria and/or hypertension, and some anticancer agents induce isolated hypertension or proteinuria leading to glomerular microangiopathy and nephrotic syndrome¹⁰⁵. Furthermore, use of drugs such as antibiotics, antivirals, antifungals, anti-inflammatory

drugs and calcineurin inhibitors may contribute to AKI in patients with cancer^{89,97}.

Pregnancy-associated AKI

Over half a million women, of whom 99% are in LMICs, die each year owing to pregnancy-related causes¹⁰⁶. In many LICs, complications of pregnancy and childbirth are the leading causes of death among women of reproductive age. Pregnancy-associated AKI is an important global public health problem that is associated with maternal and neonatal morbidity and mortality. The overall incidence of pregnancy-associated AKI during pregnancy and the postpartum period is 40–100 cases per 10,000 pregnancies^{107–114}. Postpartum pregnancy-associated AKI occurs in 16–40 people per 10,000 pregnancies and accounts for 20–50% of cases of pregnancy-associated AKI^{109,115–119}. Pre-eclampsia or eclampsia is the most common aetiology of pregnancy-associated AKI, followed by haemorrhage and sepsis^{72,92,107,108,114,116,118,120}.

Pregnancy-associated AKI varies in incidence, severity and outcome according to patient characteristics, socioeconomics, healthcare expenditure and antenatal care. An inverse relationship exists between national total health expenditure as a percentage of gross domestic product and the incidence of pregnancy-associated AKI^{121,122}.

The incidence of severe pregnancy-associated AKI, defined as AKI KDIGO stage 3, is highest in Africa, ranging from 77 to 233 cases per 10,000 pregnancies^{107,109,123,124}. The lowest incidences of pregnancy-associated AKI have been reported in HICs. However, over the past 20 years, an increasing incidence of pregnancy-associated AKI has been observed, predominantly in HICs^{120,123–125}. In the USA, the reported incidence increased from 2.29 cases per 10,000 pregnancies in 1998–1999 to 4.52 cases per 10,000 pregnancies in 2008–2009 (refs. 120,121,126). Although the reasons for this increase have not been definitively established, increases in maternal age and the prevalence of obesity have been suggested as the main drivers. The incidence of hypertensive disorders of pregnancy, including pre-eclampsia and eclampsia, has also increased in HICs, but has decreased in LMICs owing to improvements in maternal care¹²⁷.

Approximately 6–12% of pregnancy-associated AKI is associated with maternal mortality and around 25% of patients with pregnancy-associated AKI require dialysis^{118,119,128}. Pregnancy-associated AKI also increases the risk of adverse pregnancy outcomes, including miscarriage, preterm birth, stillbirth or perinatal death, by 3.5-fold compared to pregnancies without AKI. In low-resource settings, patients with pregnancy-associated AKI are often lost to follow-up and may later present with CKD^{72,92,108,120,125,129}.

AKI in liver disease

Patients with cirrhosis are prone to developing AKI, which is associated with increased hospital morbidity and mortality as well as increased risk of progression to CKD¹³⁰. A USA study that used 2004–2016 data from the National Inpatient Sample database identified >3.6 million patients with cirrhosis, of whom 22% developed AKI¹³¹. The prevalence of AKI among patients admitted with cirrhosis doubled from 15% in 2004 to 30% in 2016. Furthermore, AKI-related cirrhosis admissions were more costly and were associated with a 3.75-fold-higher risk of mortality compared with cirrhosis admissions without AKI.

Hepatorenal syndrome describes a specific phenotype of renal dysfunction observed in patients with substantial ascites and liver cirrhosis. A retrospective cohort study that included 2,063 patients with AKI and cirrhosis who were admitted to 11 hospital networks in 2019 reported that the most common aetiology was prerenal AKI (44.3%),

followed by acute tubular necrosis (30.4%), hepatorenal syndrome AKI (12.1%) and other causes (6%); 7.3% of cases of AKI could not be classified¹³². The adjusted subdistribution hazard ratio (sHR) for 90-day mortality was higher for hepatorenal syndrome AKI (sHR 2.78; 95% CI 2.18–3.54; $P < 0.001$) and acute tubular necrosis (sHR 2.83; 95% CI 2.36–3.41; $P < 0.001$) than for prerenal AKI. In an adjusted analysis, higher AKI stage and lack of complete response to treatment were associated with increased risk of 90-day mortality ($P < 0.001$ for all).

During the past decade, the diagnostic criteria for AKI and hepatorenal syndrome have undergone several revisions^{133,134}. In 2023, an expert panel from ADQI and the International Club of Ascites suggested adoption of the KDIGO criteria to define AKI in patients with cirrhosis and recommended that hepatorenal syndrome AKI should be considered in patients with cirrhosis, ascites and AKI when intravascular volume status is deemed adequate, unless strong evidence exists for an alternative explanation for AKI¹³⁵. Early recognition of hepatorenal syndrome AKI is crucial, because administration of splanchnic vasoconstrictors may reverse AKI and serve as a bridge to liver transplantation, which is the only curative option^{133,135}.

Cardiovascular-surgery-associated AKI

AKI is a common complication after cardiac surgery that affects 5–42% of patients^{136–138}. Although AKI can develop after any type of cardiac surgery, including coronary artery bypass graft procedures, procedures including valve replacement or repair and complex congenital heart surgery are associated with a higher risk of AKI. Patients with chronic cardiovascular comorbidities and CKD are at increased risk of cardiovascular-surgery-associated AKI. In its most severe form, cardiovascular-surgery-associated AKI is associated with longer hospital stays, higher healthcare costs and increased mortality^{136,139}. Notable geographic and regional differences exist in the epidemiology and outcomes of cardiovascular-surgery-associated AKI owing to variations in healthcare infrastructure, patient demographics, surgical techniques and access to healthcare resources. The highest incidences are reported in Asia and the lowest in Europe¹³⁸.

Trauma-associated AKI

The epidemiology of trauma-associated AKI varies according to multiple factors, including geographic location, patient characteristics, trauma mechanisms, severity of injury and healthcare setting. In HICs, trauma-associated AKI often results from blunt trauma (such as in car accidents and falls), whereas penetrating trauma (such as from gunshot wounds) and crush injury (such as in earthquakes) are more frequent causes in LMICs¹⁴⁰. In war or disaster zones, AKI reporting is frequently suboptimal owing to the reduced availability of reporting and clinical infrastructure. Access to emergency healthcare has an essential role in reducing the risk of development and progression of trauma-associated AKI. Among patients with trauma requiring ICU admission, the AKI incidence is ~40–50% owing to concomitant injuries, multi-organ dysfunction and the need for potentially nephrotoxic interventions¹⁴¹. By contrast, patients with trauma who do not require ICU admission have a much lower incidence of AKI (~5–10%) as their injuries are often isolated with preserved haemodynamics. Shock and high-volume blood transfusion are the most consistently reported risk factors for the development of trauma-associated AKI¹⁴². Military and disaster-related injuries (such as crush syndrome) are associated with high rates of rhabdomyolysis-induced AKI (~50–60%), whereas the risk of this aetiology is lower for civilian trauma¹⁴³. Access to emergency care, fluid resuscitation, fasciotomy and dialysis are the cornerstones

of management of rhabdomyolysis and are important in determining the outcome.

AKI secondary to tropical diseases

The environmental conditions of tropical regions contribute to various kidney-related conditions, including AKI, AKD, CKD, electrolyte imbalances and glomerular diseases. A global epidemiological study that included 4,105 cases of AKI reported that 50% of these occurred in tropical regions (19% in South Asia, 14% in Latin America and the Caribbean, 13% in Africa, and 4% in Oceania and Southeast Asia)¹⁰. Although dehydration accounted for nearly 50% of cases of AKI worldwide, the aetiology of AKI in LICs and LMICs was varied and included tropical infections (45–50%), obstetric complications (15–25%), animal envenomation or the use of traditional medicines (15–20%), and surgical or post-traumatic causes (10–15%)^{144,145}.

Common infectious causes of AKI in tropical regions include leptospirosis, malaria and dengue. The prevalence of these infections varies by region and is influenced by socioeconomic, cultural and system-level factors, including the organization of public healthcare¹⁴⁶. Leptospirosis-related AKI is particularly common in the Caribbean, Central and Latin America, South Asia, Southeast Asia and Oceania¹⁴⁷; malaria-associated AKI is very common in sub-Saharan Africa, South Asia, Southeast Asia, the Caribbean and Latin America¹⁴⁸; and dengue-associated AKI predominantly affects the Caribbean, Latin America and Southeast Asia¹⁴⁹.

Leptospirosis is a notable zoonosis that is prevalent in tropical areas but has also been reported sporadically in HICs owing to global travel. Infection can lead to Weil syndrome, which is a severe condition characterized by AKI and icteric leptospirosis. The incidence of AKI in patients with leptospirosis can be as high as 84%^{150–154}. AKI is caused by direct and indirect effects of leptospirosis, including dehydration, rhabdomyolysis and bleeding^{155,156}.

Malaria is endemic in tropical and subtropical regions and is caused by five *Plasmodium* species: *P. vivax*, *P. falciparum*, *P. malariae*, *P. ovale* and *P. knowlesi*. The incidence of malaria-associated AKI varies from 0.5% to 30%, depending on patient demographics and AKI diagnostic criteria^{149,157}. In 2015, the majority of malaria-related deaths occurred in Africa (90%), followed by those in Southeast Asia (7%) and the Eastern Mediterranean (2%)¹⁴⁹.

An estimated 2.5 billion people in tropical and subtropical regions are at risk of dengue viral infection¹⁵⁸. The 2011 World Health Organization guidelines coined the term ‘expanded dengue syndrome’ to incorporate a wide spectrum of unusual manifestations of dengue infection that affect various organ systems, including the kidney, liver, heart and brain^{158,159}. A systematic review reported that renal involvement in dengue infection varied from glomerulonephritis to nephrotic range proteinuria and AKI¹⁵⁸. The researchers found that AKI among patients with dengue was associated with substantial morbidity, mortality and longer hospital stays, resulting in an increased financial burden for patients and healthcare systems.

Snakebites account for 70% of community-acquired AKI in Myanmar, 2–3% in India and 1–2% in Thailand. The incidence of snakebite-associated AKI ranges from 1.4% to 38%, with mortality of 1–20%, depending on the snake species^{160,161}. AKI typically occurs within hours of a snakebite but can also develop days later. The mechanisms of injury include both direct and indirect effects, such as dehydration, haemolysis, rhabdomyolysis and disseminated intravascular coagulation. Wasp and bee stings are also important causes of AKI, particularly in South Asia and Latin America. Data from China suggest that the

severity of the clinical manifestations correlates with the number of stings, with severe systemic symptoms – including kidney and liver injury – generally occurring after ≥ 10 stings¹⁶².

Tropical plants that contain nephrotoxins that cause AKI include djenkol beans, impila (*Callilepis laureola*), starfruit (*Averrhoa carambola*), poisonous mushrooms (*Amanita phalloides*), cottonseed oil (gossypol, which causes hypokalaemia and distal renal tubular acidosis) and Chinese herbs containing aristolochic acid, which induces tubular atrophy and interstitial fibrosis^{163–169}. Consumption of these toxins highlights the intersection of cultural practices, traditional medicine and environmental factors in the epidemiology of AKI in tropical regions.

Knowledge and practice gaps that must be addressed to improve AKI care

Global disparities in AKI care exist owing to differences in healthcare systems, availability of resources, socioeconomic factors and environmental challenges. Context-specific, equitable strategies, including attention to patient perspectives, combining education, advocacy, innovation, leadership, resource allocation and political commitment, are required to improve recognition and management of AKI worldwide.

The 5R approach for early identification and management of AKI

The 5R approach – risk, recognition, response, renal support and rehabilitation – provides a framework for holistic care across the continuum of AKI. Implementing the 5R strategy across diverse populations worldwide requires careful consideration of differences in healthcare, disease prevalence, resource availability and patient values¹⁷⁰ (Table 1). Existing disparities present substantial challenges for the prevention, early detection and management of AKI, but also opportunities for action²⁹.

Risk: understanding regional variability in AKI predisposition.

AKI risk depends on the severity of the nephrotoxic insult and the susceptibility of the patient^{171–175}. Socioeconomic status, access to healthcare, environmental exposures, prevalence of chronic diseases and the impact of climate change also have important effects^{26,176}. As mentioned above, in LMICs, infectious diseases and limited access to healthcare are prominent risk factors for AKI, whereas in HICs, AKI is more often associated with sepsis, major surgery and nephrotoxic agents^{157,177}.

Recognition: improving early detection of AKI in diverse healthcare settings.

AKI is often under-recognized or poorly identified. One reason for this lack of detection is that the traditional biomarkers, SCr and urine output, are not very specific³³. Alternative biomarkers have shown promise in improving the early detection of AKI, but their implementation varies worldwide^{178–180}. In HICs, advanced diagnostic tools and EHR integration have facilitated the early identification of AKI, while in LMICs, the lack of access to such technologies hinders timely diagnosis¹⁸¹. The use of simple point-of-care testing technologies for AKI (such as dipsticks for the detection of proteinuria, serum creatinine, salivary urea nitrogen and electrolytes) is attractive for LMICs, where access to hospital laboratories may be limited, but more research is necessary to determine the role of these tools^{52,182–187}. The International Society of Nephrology Oby25 initiative (which aimed to eliminate preventable AKI deaths by 2025) demonstrated that use of locally adapted point-of-care tools for identification of AKI together

Table 1 | Considerations for implementation of the 5R approach for early identification and treatment of AKI in diverse populations

5R category	Knowledge	Practice gaps	Key factors	Potential solutions
Risk	Risk factors vary substantially Most existing risk scores are based on cardiac surgery or coronary angiography cohorts	Lack of validated tools for individual risk assessment Limited risk scores for non-cardiac surgery settings Socioeconomic determinants of risk are underexplored	Baseline kidney function Severity of nephrotoxic exposure Patient susceptibility Socioeconomic disparities Climate change	Development of risk scores for personalized risk stratification using artificial intelligence Integration of socioeconomic factors in evaluations Development of region-specific risk-stratification tools Patient advocacy Training and education
Recognition	AKI is often underdiagnosed despite improved diagnostic tools Early recognition is critical for timely interventions and better outcomes	Inconsistent availability of diagnostic tools Limited use of clinical alerts Variability in staff training	Use of traditional and novel biomarkers Access to trained personnel and diagnostic systems Effectiveness of AKI alerts	Adoption of affordable biomarkers and point-of-care technologies Integration of advanced biomarkers into standard practice Deployment of artificial-intelligence-driven alerts for early recognition Telemedicine Enhanced staff training programmes Patient advocacy
Response	Timely interventions improve outcomes, particularly for specific AKI subphenotypes	Limited tools to identify AKI subphenotypes in clinical practice Limited tailored intervention strategies Limited integration of drug stewardship into routine AKI management	AKI subphenotypes Healthcare resource availability Evidence-based pharmacological interventions	More research into AKI subphenotypes Tailored interventions based on resource availability Application of telemedicine for timely interventions Strengthening of drug stewardship Enhanced education programmes for healthcare teams Development of specialized tertiary hospital centres that are telemedicine enabled
Renal support	Access to KRT is inequitable globally Lack of KRT leads to high mortality in low-resource settings	Uncertainty about optimal KRT strategies for different AKI types Insufficient tools for monitoring renal recovery Scarcity of trained personnel and devices for KRT	KRT device availability Trained healthcare providers Cost-effective resource allocation	Global KRT device distribution Increased training opportunities for healthcare providers KRT protocols adapted to local resources and customs Development of quality metrics and audit criteria Global expansion of cost-effective KRT technologies Strengthening of supply chains for KRT consumables
Rehabilitation	Structured post-AKI care, including nephrology follow-up, improves long-term outcomes Diverse appreciation of the importance of AKI follow-up among patients and clinicians	Inadequate identification of patients who benefit from follow-up Unclear consensus on the optimal type and duration of post-AKI care	Patient education and advocacy Tools to identify at-risk survivors Integration of AKI follow-up with care of other comorbidities	Research to optimize follow-up strategies Enhanced awareness programmes for patients and providers Development of tools to identify high-risk survivors Establishment of structured post-AKI care clinics Advocacy for long-term funding for AKI survivors

AKI, acute kidney injury; KRT, kidney replacement therapy.

with a training programme to optimize AKI identification and management can improve the coordination of care of patients and outcomes in remote and resource-scarce settings²⁹.

Response: tailoring interventions to regional healthcare capabilities. The response to AKI involves appropriate interventions to identify the aetiology, prevent progression, reduce morbidity

and facilitate renal recovery. The specific actions depend on the available healthcare infrastructure, resources and patient characteristics, including potentially modifiable factors. Rapid response teams and early intervention protocols are more readily available in HICs than in LMICs¹⁸⁸. Biomarker-guided management has been proposed to prevent AKI progression following major surgery and in patients receiving nephrotoxic drugs¹⁸⁹. In LMICs, resource

constraints necessitate a more pragmatic approach for prevention of AKI and reducing progression to CKD, with a focus on basic supportive care¹⁹⁰.

An important global challenge that must be addressed to improve care is the lack of awareness of AKI among healthcare providers. Educational interventions have proved effective. For example, in Malawi, a nurse-led educational initiative significantly improved the attitudes of healthcare workers towards detecting and managing AKI and led to improvements in care processes^{29,61}. To be effective, such educational programmes must be combined with the provision of the necessary resources and regular evaluations. Another key issue is establishing

quality metrics for AKI management that can be implemented across different settings based on the available resources^{66,191,192} (Table 2).

Renal support: addressing disparities in access to KRT. KRT is a cornerstone of the management of severe AKI, but access to dialysis is highly variable worldwide. In many LMICs, high costs, lack of infrastructure and workforce shortages limit the availability of KRT^{49,193}. For example, substantial inequalities in KRT exist in the BRICS nations (Brazil, Russia, India, China and South Africa), caused primarily by varying levels of economic development and healthcare investment¹⁹⁴. The Oby25 initiative highlighted disparities in access to dialysis for

Table 2 | Interventions and quality metrics for sustainable AKI care

5R category	Region	Structure	Process	Outcome
Risk stratification	Global	Encourage risk assessment at admission, regardless of technology; use manual checklists if digital tools are unavailable	Identify and communicate modifiable AKI risk factors to patients and staff; use paper-based or verbal tools if needed	Monitor and audit high-risk exposures periodically; prioritize education of frontline providers
	Low resource	Set up community-level outreach and small-scale registries of high-risk populations	Set up health campaigns on pregnancy, trauma, dehydration and nephrotoxin risks	Identify proportion of patients at risk of AKI; collect number of outreach referrals
	High resource	Implement integrated EHR and clinical-decision-support tools	Implement digital pharmacy alerts, automated risk scoring and EHR-based flagging	Use automated interventions and surveillance tools
Recognition	Global	Use early warning criteria; implement triggers for escalation	Train providers to recognize early signs of AKI; encourage prompt documentation regardless of system	Improved AKI documentation and staging in all patients admitted to hospital
	Low resource	Point-of-care or salivary creatinine testing; essential laboratory and data infrastructure	Mobile phone AKI detection reporting; clinician education for AKI detection; designated AKI screener	Earlier and more efficient detection of AKI and risk factors
	High resource	EHR alerts; real-time dashboards; biomarker panels	Automated AKI alerts; modifiable risk factor recognition and mitigation	Earlier recognition of AKI; automated prompt for documentation; rapid semi- or fully automated AKI staging and interventions
Response	Global	Create and share standard AKI response protocols across departments	Ensure basic AKI interventions are applied routinely	Reduction of delays or gaps in management regardless of setting
	Low resource	Access to specialty care	Use of AKI care bundles; fluid protocols; infection control protocols	Lowered incidence of AKI, its progression or complications
	High resource	Bundled order sets; automated care bundles; integrated treatment alerts	Early goal-directed therapy; remote nephrology input; telemedicine	Improved response times and better AKI outcomes
Renal support	Global	Agree referral criteria and access pathways for patients requiring KRT	Monitor fluid balance, electrolytes and creatinine trends; adjust treatments accordingly	Improved KRT outcomes
	Low resource	Educate and prepare for at least one mode of KRT	Remote triage for KRT; locally sourced KRT fluids	Proportion of patients who receive KRT increased to the proportion who have indications for KRT
	High resource	Diversity of KRT modalities and expert teams	Protocolized continuous-KRT initiation; access to transplant programme	Improved KRT adequacy metrics
Rehabilitation	Global	Plan structured follow-up within 1–3 months of AKI	Reinforce patient education on sick-day rules and follow-up laboratory results regardless of resource level	Improved re-hospitalization or mortality rates
	Low resource	Educate and utilize community health workers	Text-message reminders; education on nephrotoxin avoidance	Lower risk of CKD progression
	High resource	Post-AKI clinics; multidisciplinary teams; remote patient monitoring; CKD transition programmes	EHR alerts; virtual nephrology follow-up; use of artificial intelligence in prediction of AKI recurrence or CKD development	Improved re-admission rates and CKD progression metrics

AKI, acute kidney injury; CKD, chronic kidney disease; EHR, electronic health record; KRT, kidney replacement therapy.

children with AKI in lower-resource settings^{15,17,52}. Globally, millions of deaths each year are thought to result from a lack of access to KRT^{4,195}, but many deaths in LMICs are not recorded. Efforts to expand access to KRT in resource-limited settings have achieved some success, but important challenges remain, including the high cost of equipment, limited availability of trained personnel, the need for adaptation to local conditions and socioeconomic factors¹⁹⁶.

Rehabilitation: promoting recovery and reducing AKI sequelae.

Although no consensus criteria exist, renal recovery is often described as complete versus partial resolution of kidney dysfunction, and AKI is often described as transient (resolving within 48–72 hours) or persistent^{197,198}. In a retrospective cohort study of 16,968 critically ill patients with stage 2 or 3 AKI, 41% had not fully recovered kidney function at the time of hospital discharge¹⁹⁹. Of these patients, 26% had no AKI reversal at any point, and 15% had AKI reversal but subsequently relapsed and did not recover kidney function.

The presence or absence of renal recovery and its timing have prognostic implications. Compared to recovery within 10 days, later recovery is associated with an increased risk of progressive decline in kidney function²⁰⁰. The risk of CKD increases with greater KDIGO AKI stage in a graded fashion. Pre-existing kidney dysfunction may also contribute to the risk of long-term kidney function decline^{201,202}. In addition to long-term adverse kidney outcomes, AKI survivors are at increased risk of hypertension, cardiovascular disease, impaired quality of life and short-term mortality^{203–205}. A 2025 study that included >65,000 patients with stage 2 or 3 AKI reported that 12.4% had severe persistent AKI (defined as stage 3 AKI that persisted for >72 h), which was associated with a 1.5-fold higher risk of 90-day mortality, a 2-fold higher risk of hospital readmission and a significantly reduced likelihood of kidney function recovery²⁰⁶. These findings highlight the importance of non-recovery from AKI and its influence on healthcare utilization, costs and outcomes^{207,208}.

Effective models of care to improve long-term outcomes of AKI remain unclear²⁰⁹. In HICs, multidisciplinary care teams, including nephrologists, dietitians, psychologists and rehabilitation specialists, are often involved²¹⁰. Similar services are often scarce in LMICs. Although nephrology follow-up and structured post-AKI clinics have been associated with improved outcomes, aftercare by specialists remains challenging to coordinate worldwide^{211,212}. Furthermore, some patients prioritize other health conditions over their kidney disease, have limited awareness of AKI as a potential long-term health issue and experience anxiety caused by competing health demands²¹³. The National Institutes of Health (NIH)-funded Caring for Outpatients after Acute Kidney Injury (COPE-AKI) trial (NCT05805709) is evaluating whether a multimodal intervention can improve outcomes among patients with persistent stage 2 or 3 AKI²¹⁴. Patients are randomly assigned to either an intervention group – receiving physician oversight and discharge recommendations, nurse navigator support for education and care coordination, and pharmacist-led medication review – or a usual care group, which receives information on kidney disease, nephrotoxin avoidance and the importance of follow-up. The results are expected to inform best practices for post-discharge care in patients with AKI.

The 5R approach to AKI provides a comprehensive framework for AKI care, but its effectiveness is contingent on healthcare infrastructure, resource availability, disease burden and socioeconomic factors. The Oby25 non-randomized trial showed that point-of-care testing together with an education and training programme for physicians

and care providers improved the recognition and management of AKI in healthcare centres in Malawi, Bolivia and Nepal, and resulted in fewer hospitalizations and reduced mortality²⁹. A need exists for sustainable, region-specific multidisciplinary initiatives and innovative approaches to bridge the gaps in AKI care in diverse populations and regions (Table 1).

Health equity

Equitable deployment of medical care is the focus of an increasing number of global initiatives in both general and acute care medicine. However, people with low health literacy and those in low-income and resource-limited settings have a disproportionate burden of disease. Differences in access to primary healthcare, education and preventative strategies are major contributors. The relationship between socioeconomic status and kidney health is bidirectional, with the risk of poverty increasing as kidney disease progresses²¹⁵. In many countries, the direct and indirect costs of kidney care are paid out-of-pocket, putting patients at risk of rapid impoverishment²¹⁶. A systematic review that compared the out-of-pocket payments for various conditions identified kidney disease as the leading cause of catastrophic health expenditure across lower-resource settings²¹⁶. As a result of lack of funding, care often focuses on acute management rather than prevention^{217–220}. Three factors that can be addressed to improve AKI health equity are access to care, advocacy and agnostic determination of injury state.

Access to care. Access to care is a factor that can be addressed when attempting to achieve equity in AKI care. In particular, low access to SCr measurement outside hospital settings is well recognized as a driver of inequity. A 2018 study reported that two-thirds of LICs were not able to measure SCr in primary care and no LICs were able to provide quantitative albumin or protein urinalysis²²¹. Reliance on hospital-based physicians and subspecialist nephrologists may propagate inequity given that the nephrology workforce is unequally distributed worldwide, with more nephrologists in HICs than in LMICs. Increasing access to AKI care can be achieved by empowering rural healthcare clinics to screen for and educate people about AKI, utilizing mobile health platforms for patients to self-diagnose and track AKI symptoms¹⁸¹, and moving front-line care for AKI to primary care clinicians. These initiatives could help to reduce inequity by focusing on individuals with lower socioeconomic status and lower rates of education and employment as well as areas of the world where cultural beliefs limit access to healthcare²²².

Advocacy for AKI. AKI advocacy can be improved by increasing knowledge of the importance of kidney health. Medical societies within nephrology, primary care, emergency medicine and critical care should ensure that local governments and hospital leadership understand the costs and burden of AKI. Crucial in this knowledge dissemination is utilization of the concept of ‘opportunity costs’ – the potential savings to hospital systems that can be achieved through proactive disease recognition and AKI mitigation²²³. Early identification of AKI is vital, but should be part of a broader strategy focused on strengthening the entire healthcare system to prevent AKI in the first place. Most aetiologies of AKI can be prevented by interventions at the individual, community, regional and in-hospital levels²²⁴. Efforts should focus on addressing risk factors, improving access to care and implementing preventative measures alongside diagnostic tools. In this regard, education delivered by clinical teams throughout the clinical environment, at the bedside and to patients directly is important worldwide. The exchange of knowledge and innovation between HICs and LMICs can

also promote good practices. Investment in registries and systems to collect data to understand the burden of AKI and associated outcomes is vital to inform public health policy, allocate resources and support priority setting.

Agnostic determination of AKI. Agnostic determination refers to methods of diagnosing or identifying AKI that do not rely solely on traditional markers such as SCr or urine output. Current definitions of AKI may disadvantage certain patient groups, including women, children and people with muscle disorders, exacerbating sex- and age-based inequities in healthcare^{54,225}. The addition or exclusion of race from glomerular filtration rate equations is also controversial, because biases may be introduced with either approach²²⁶. Body mass index influences creatinine generation, complicating evaluations in patients with obesity or underweight^{227,228}. An agnostic approach aims to detect AKI regardless of the cause, clinical setting or underlying disease. Machine learning and artificial intelligence models trained on large datasets have been shown to detect patterns suggestive of AKI based on subtle changes in laboratory values, vital statistics or EHR data without needing specific clinical context²²⁹.

All individuals concerned with kidney health and kidney care (including non-professionals) have a responsibility to be aware of and to create awareness of health inequities. Solutions require leadership, responsibility, education, advocacy, innovation and political will¹⁷⁵. Innovation should not only focus on sophisticated technologies but also include the development of approaches to improve the uptake of prevention strategies and the accessibility and delivery of primary care.

Patient perspectives for AKI care

Many patients are unaware that they have had AKI. Communication gaps between hospital teams and between healthcare providers and patients exacerbate this issue²³⁰. In an online survey of 124 adult survivors of AKI, only 52% rated communication with their medical team as very or extremely good²³¹. Another study noted that >80% of patients with AKI did not receive AKI education upon hospital discharge, which contributed to high readmission rates²³².

Importantly, patient priorities do not always align with those of healthcare providers. Moreover, the decisions of an individual about their healthcare are influenced by many factors, including their understanding of their health, finances, social support, geography, culture, beliefs and freedoms. AKI survivors have described impaired participation in life, unbearable treatment burden, financial pressures and anxiety²³³. Other challenges include prioritization of other health conditions over their kidney disease, limited awareness of AKI as a potential long-term health issue, logistical and emotional challenges and anxiety caused by competing health demands^{213,234}. Healthcare providers must appreciate these overarching determinants to consider patients holistically and avoid contributing to health inequities. A systematic review of 20 qualitative studies and surveys that reported the perspectives and experiences of adults with AKI concluded that providing education, alleviating treatment burden, and implementing a comprehensive model of care may help to address the needs of these patients and lead to better outcomes²³³.

Improving AKI care through implementation science demands a unified vision and collaboration across all stakeholders. Patient and family advocates have a critical role in ensuring that evidence-based practices are tailored to real-world needs and genuinely improve patient outcomes. Several avenues for patient engagement and empowerment can be considered. Involving patients and families in research

teams, safety councils and care committees ensures that their perspectives can shape every stage – from identifying care gaps to planning, executing and evaluating new practices.

Progress in AKI care is hindered by the lack of meaningful trial end points, and traditional clinical metrics often miss what matters most to patients, such as recovery, long-term health, dialysis dependence and survival. Innovations in clinical trial design (including the use of biomarkers, novel approaches to processing of statistical data, the use of patient-centred trial end points, the design of collaborative models, and learning from other disciplines such as cardiology and oncology) are essential to move from stagnation to a rapid improvement in AKI care. A structured process should gather and evaluate new and existing initiatives for AKI care, actively involving patients, families and experts to identify priorities and barriers. Their insights will guide the development and implementation of effective, patient-centred care strategies, driving real progress in AKI outcomes.

Creating a sustainable infrastructure to address the burden of AKI

A sustainable infrastructure for AKI care is essential to mitigate the burden of AKI for patients and healthcare systems. Such an infrastructure requires consideration of healthcare policies, social determinants of health, health inequities and environmental factors as well as the application of digital health tools and the development of targeted therapies (Fig. 3).

Economic burden and healthcare policies

AKI represents a substantial economic burden for healthcare systems worldwide, with a mean annual per-patient cost of approximately US\$5,975 (refs. 124,235–241). The substantial costs of AKI are associated with its management and subsequent chronic conditions. The immediate costs include hospital and intensive-care-related expenses, including KRT²⁴². Owing to the complexity of care required, AKI-related hospitalizations can be up to three times more costly than non-AKI hospitalizations. AKI also incurs considerable indirect costs, including lost productivity, long-term disability, diminished patient quality of life and healthcare needs related to CKD²⁴³.

By implementing standardized care protocols and early detection strategies, such as continuous quality assurance programmes that use biomarkers and EHRs, hospitals can lower the incidence and severity of AKI, thus reducing the direct and indirect costs of AKI care^{78,244,245}. For example, integrating AKI alert systems within EHRs to provide real-time notifications to clinicians could facilitate early intervention, potentially preventing the onset or exacerbation of AKI²⁴⁶. The use of AKI care bundles in specific high-risk patients has also been demonstrated to improve outcomes and reduce costs by minimizing complications and shortening hospital stays. In LMICs, similar strategies that are less resource-intensive could be used. For example, monitoring of SCr and/or urine output among high-risk patients in healthcare settings could enable earlier identification of AKI and implementation of care bundles, which are considered essential steps towards AKI prevention. The heterogeneity of epidemiology studies and care resource availability around the world requires adjustments to reflect the realities of specific settings¹⁹².

Healthcare delivery and expenditure depend on regional healthcare infrastructures and governance. Therefore, AKI-care-related policies need to be addressed globally. Policymakers can have a crucial role in reducing the economic burden of AKI by promoting the adoption of standardized diagnostic criteria and treatment

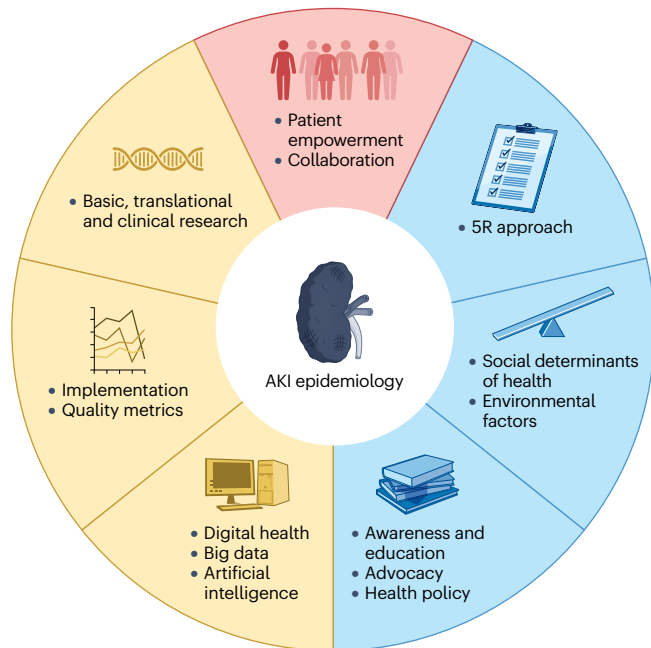


Fig. 3 | Opportunities for sustainable improvements in AKI care. Factors that must be addressed to improve recognition and management of acute kidney injury (AKI) worldwide include social determinants of health, environmental factors, patient empowerment, application of the 5R approach (risk, recognition, response, renal support and rehabilitation) for early identification and treatment of AKI, AKI advocacy, awareness and education, health policy, digital health approaches, implementation quality metrics and basic, translational and clinical research. These areas require multidisciplinary collaborative efforts and can be achieved with concerted coordinated efforts.

protocols, ensuring equitable access to preventive and therapeutic interventions, and incentivizing research into and development of approaches and therapies. Furthermore, policies that support the integration of digital health tools in clinical practice could potentially enhance the efficiency and effectiveness of AKI management by empowering patients in their own care, improving clinician performance, providing individualized precision medicine for the care of patients with AKI, and helping local providers to provide high-quality care.

Social determinants of health

The World Health Organization defines social determinants of health as non-medical factors that influence health outcomes, including age, sex and gender, income and social protection, education, food security, and access to healthcare. Growing evidence supports the association between social determinants of health and the epidemiology of AKI. In the Oby25 multinational, cross-sectional study, community-acquired AKI and dehydration occurred more often in LMICs than in HICs, and SCr concentrations at dialysis initiation were higher, continuous KRT utilization was lower, and mortality was higher in LMICs than in HICs^{15,17,177}. Furthermore, a US study reported that the incidence of community-acquired AKI was higher among African American participants (7.4 cases per 1,000 person-years) than among white participants (5.8 cases per 1,000 person-years)²⁴⁷. Adjustment for income and/or insurance status attenuated the association between African American

race and AKI, suggesting that socioeconomic status, rather than any genetic difference, influences the incidence of AKI²⁴⁷.

Addressing health inequities

The sustainable development goals were adopted by all United Nations member states in 2015 as part of the 2030 agenda for development to end poverty, fight inequalities and tackle climate change²⁴⁸. One of the most important targets was achieving universal health coverage by facilitating access to the full range of health services whenever and wherever people need them without financial hardship. Although advancing access to healthcare is critical in improving patient outcomes, multi-faceted work on a global scale is required to recognize and understand health inequities and how they affect AKI care. Kidney diseases have not historically been recognized as global health issues, with the emphasis placed on other non-communicable diseases such as diabetes, cardiovascular disease and cancer. Raising awareness through professional societies and patient advocacy groups is crucial to ensure that kidney diseases are prioritized.

Infections, volume depletion from diarrhoeal illnesses, and pregnancy-related factors are common causes of AKI in LMICs¹⁹⁰. National policies should, therefore, focus on surveillance and screening strategies such as the prevention of infectious diseases through vaccination programmes, sanitation, and the supply of clean water. Improving obstetric care through early referral of women at high risk of pregnancy-associated AKI, provision of resources to ensure adequate infrastructure to provide appropriate treatment, and training of healthcare professionals is urgently required to address these inequities.

The Oby25 initiative aimed to eliminate preventable deaths from AKI by 2025, emphasizing a global framework that includes increasing awareness and education within the healthcare community, improving diagnostic and treatment protocols, enhancing access to care, and investing in research and innovation to identify global strategies for the early prevention, management and diagnosis of AKI worldwide, particularly in LMICs^{29,52,170,177,249}. This programme highlighted the need for collaboration between high-income and low-income regions to overcome disparities.

In 2016, the International Society of Nephrology launched the Global Kidney Health Atlas to assess the global status of AKI and CKD care and guide policy improvements²⁵⁰. Surveys conducted across ten International Society of Nephrology regions provided comprehensive data on kidney healthcare delivery. In 2022, a survey that included 167 countries – representing 97.4% of the global population – reported that only 4% had national AKI detection programmes (half of which relied on reactive identification through clinical practice) and only 19% of governments recognized AKI as a healthcare priority⁵¹ (Fig. 4). Although 98% of countries could provide acute haemodialysis for AKI, 31% lacked access to peritoneal dialysis. Public funding for acute haemodialysis or peritoneal dialysis was available in 44% of countries, but funding availability varied widely by region (from 17% of countries in Oceania and Southeast Asia to 91% of those in Western Europe) and increased with country income level. Despite initiatives such as the Oby25 campaign, the capacity for optimal AKI care remains low, particularly in LMICs. The survey highlighted persistent gaps in funding, infrastructure, workforce, health information systems and national strategies, emphasizing the need for coordinated global action to improve AKI outcomes.

The Global Kidney Health Atlas findings emphasized that AKI management tools and guidelines must be adapted to local needs, with a clear progression of care practices. The Global Kidney Health Atlas

found limited adoption and awareness of AKI guidelines^{51,250}, whereas the Oby25 initiative demonstrated that improving caregiver awareness of AKI improves outcomes such as hydration, hospitalizations and mortality²⁹. Early AKI detection and management depend on available resources and must be tailored to each setting. Together, these initiatives support better data collection and the development of sustainable advocacy and policy efforts, particularly in LICs and LMICs. Key recommendations from these studies include: engaging local resources and thoroughly assessing the scope of AKI and potential solutions; deepening understanding of local and regional conditions to guide effective public health strategies; training local healthcare providers to conduct research and develop evidence-based, context-specific solutions; and collaborating with regional and international programmes sharing similar goals (such as malaria control, clean water access, World Health Organization initiatives and non-communicable disease campaigns). These approaches aim to build regionally appropriate, sustainable AKI management systems and improve patient outcomes globally.

Environmental factors and climate change

Environmental factors are increasingly recognized as critical contributors to the incidence and severity of AKI. Extreme weather events (such as heatwaves, floods and droughts) heighten the risks of dehydration and heat stress, which are important precursors to AKI^{251,252}. Environmental factors influence water quality and pollution, leading to increased exposure to nephrotoxic substances such as heavy metals, pesticides and industrial chemicals. Contaminated water sources, particularly in resource-limited settings, pose substantial risks by directly causing kidney damage or contributing to conditions that elevate AKI risk.

Climate change and the global increase in average temperature also influence the development of AKI. In a cross-sectional study of 1,114,322 patients in New York State, USA, extreme heat exposure was significantly associated with a greater risk of emergency department visits for kidney disease¹⁸¹. Another report from Texas, USA, found that each 1 °C increase in temperature was associated with a 1.73% (95% CI 1.43–2.03) increase in hospital admissions related to all types of kidney disease, with an even stronger relationship with AKI (3.34% (95% CI 2.86–3.82))²⁵³. Hypovolaemia, heat-related illness-associated rhabdomyolysis and inflammation have been suggested as the underlying pathophysiological mechanisms of this increase. Emergency department visits for urinary tract infections and kidney stones are also influenced by climate change. Older patients with multiple comorbidities, users of drugs that interfere with thermoregulation (such as alcohol, anticholinergics or antidepressants), outdoor labourers and minoritized ethnic groups are particularly vulnerable^{251,254}. Low income, poor health and residence in areas with limited access to air-conditioning contribute to increased susceptibility to heat-related illnesses²⁵⁵.

Climate change is expected to cause shortages of food and clean drinking water as well as increases in the prevalence of AKI owing to water- and vector-borne diseases such as leptospirosis, schistosomiasis, malaria, dengue fever and Zika virus¹⁴⁹. The geographic spread of leptospirosis, malaria, dengue and Zika virus is expanding owing to climate-driven changes in animal migration and habitats, resulting in an increase in the prevalence of AKI even in non-tropical regions. These factors, coupled with access to immunologically naive animals that are susceptible to infection, may contribute to the emergence of vector-borne diseases in non-tropical regions¹⁴⁹. Other challenges relate to changes in infrastructure, such as the destruction of healthcare centres during floods or earthquakes.

Effective mitigation of environmental factors and climate change requires coordinated efforts among environmental scientists, healthcare providers, policymakers and communities. Integrating health considerations into climate policies and developing robust healthcare systems are foundational steps in addressing these issues²⁵³. Public health initiatives must ensure access to clean water, promote hydration, and enforce occupational safety regulations to prevent heat-related AKI^{252,256}. International agreements, such as the Paris Climate Accord (<https://unfccc.int/process-and-meetings/the-paris-agreement>), and collaborative efforts between governments, non-governmental organizations and the private sector are essential for developing and implementing effective strategies to reduce the impacts of climate change on kidney health. By recognizing and addressing the multifaceted environmental factors that contribute to AKI, stakeholders can develop more resilient health systems and targeted interventions to protect at-risk populations in the changing climate²⁵⁰.

Digital health tools

In the past few decades, developments in digital technologies and the ever-growing availability of digital data have brought digital health to the forefront of attention for research and development in medicine. The spectrum of digital health solutions for AKI spans from identifying high-risk patients in communities and hospitals to detecting those who already have AKI and providing timely, efficient and evidence-based care during and after their medical encounters¹⁸¹. Advances in generative artificial intelligence provide opportunities to use unstructured and structured data without a substantial need for curation to improve

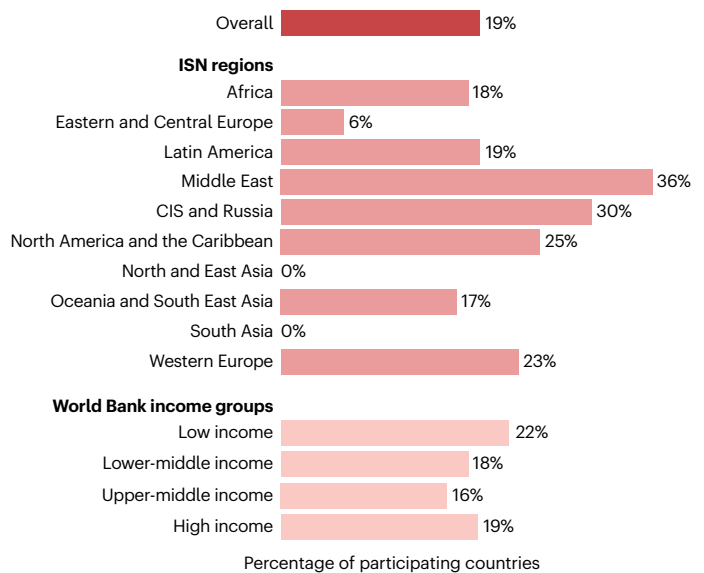


Fig. 4 | Recognition of AKI as a government health priority in different regions and income groups. A 2022 survey reported that the governments of only 30 of 162 participating countries (19%) recognized acute kidney injury (AKI) and/or its treatment and prevention as a health priority. The recognition of AKI as a health priority varied between International Society of Nephrology (ISN) regions and was greatest in the Middle East ($n = 4$, 36%); the Commonwealth of Independent States (CIS) and Russia ($n = 3$, 30%), followed by North America and the Caribbean ($n = 3$; 25%). The recognition of AKI as a health priority was low in all World Bank income groups: low-income countries ($n = 4$; 22%); lower-middle-income countries ($n = 8$; 18%), upper-middle-income countries ($n = 6$; 16%) and high-income countries ($n = 12$; 19%). Reproduced with permission from ref. 51.

the prediction, detection and management of people with AKI and AKD²⁵⁷. In addition, these tools, including large language models, can enhance communication across different cultures, languages and populations. These capacities could aid concerted efforts in the global management of AKI.

Importantly, the development, implementation and marketing of digital health tools could also exacerbate disparities in care and result in potential harm to underprivileged patients. Almost all of the available digital health solutions have been developed and tested in resource-rich academic institutions¹⁸¹, and most are based on extant data in EHRs. The availability of EHR systems across the globe is very variable. Most resource-rich countries use advanced proprietary EHRs, whereas many countries and institutions with limited resources would benefit from access to EHRs or open-source EHR systems²⁵⁸. To generalize the use of digital health solutions and avoid increasing healthcare disparity, it is essential to expand the infrastructure needed for these solutions, develop and validate them in underserved areas, and ensure their appropriate implementation, maintenance and calibration to fit the needs of patients in each region.

Access to the internet is also essential for digital health solutions to perform appropriately. The Internet of Things is a network of devices that can exchange data with each other and the cloud. An Internet of Things consisting of sensors, software and objects that enable patient empowerment, clinical diagnosis, monitoring, follow-up, therapeutics and hospital and/or outpatient clinical care could be used as a resource to improve AKI care¹⁸¹. Unfortunately, substantial digital divides exist between and within countries as well as between sexes, age groups, cities and rural areas and types of internet connection (for example, optical fibre versus 3G). The United Nations International Telecommunication Union global connectivity report showed a substantial increase in global internet access to 70% of people in 2023 (ref. 259). However, access was higher among men (70%) than women (65%), with a greater gender gap in LMICs; among those aged 15–24 years (71%) compared with other age groups; and in urban (81%) versus rural areas (50%), with considerably larger gaps in LICs. In HICs, internet access was equal or nearly equal in urban and rural areas, whereas in LICs, residents in urban areas were 3 to 3.5 times more likely to have internet access than those in rural areas. Moreover, only 35% of people worldwide had access to 5G in 2023 (ref. 259). Achieving the goals of the United Nations International Telecommunication Union – universal internet access, universal and affordable broadband coverage, universal ownership and access to internet-enabled devices and internet access for all schools – is imperative to realize the capabilities of digital health solutions in underprivileged regions.

Targeted therapies

Extensive efforts have been made to develop targeted therapies to reduce the incidence, severity and duration of AKI episodes and progression from AKI to CKD, with limited success. A major challenge is the vast heterogeneity of the populations studied and the aetiology and mechanisms of AKI. Most of the data on AKI incidence is derived from the analysis of patients in ICUs in HICs, but many cases of AKI occur in the community, particularly in LMICs. Some common risk factors for AKI, such as infections, can be identified across countries, enabling the development and standardization of approaches for early recognition, but substantial variations exist⁵².

A possible approach to overcoming cohort heterogeneity is to improve trial design and the application of enrichment strategies for patient selection on the basis of phenotype and/or biomarkers, in

order to reduce heterogeneity and increase statistical power²⁶⁰. Prognostic enrichment strategies enable the selection of a subgroup of patients with a higher probability of reaching the primary end point. Conversely, predictive enrichment strategies increase the probability that a specific intervention will have beneficial effects¹⁸⁰. The key element of these enrichment strategies is the identification of a subphenotype within a cohort of patients with distinctive clinical features or biological mechanisms involved in a disease phenotype (endotype)²⁶¹.

Use of biomarkers of tubular stress (such as TIMP-2 or IGFBP7) and injury (such as NGAL) are promising enrichment strategies to identify subgroups of patients at increased risk of AKI. The single-centre PrevAKI trial of a KDIGO bundle of care (comprising stringent control of haemodynamics, volume status, glycaemia and avoidance of nephrotoxic drugs) enrolled patients undergoing cardiac surgery who were defined as being at high risk of AKI on the basis of a ratio of urinary levels of TIMP-2 to IGFBP7 of >0.3. Although the overall incidence of AKI was similar in the intervention and control groups (46.3% versus 41.5%), the incidence of moderate and severe AKI was significantly lower in the intervention group than the control group (14.0% versus 23.9%; $P = 0.34$)^{262,263}. In the same clinical setting, the cardiac-surgery-associated NGAL score may enable easier identification of patients with acute tubular damage (subclinical AKI) and permit an earlier preventive strategy after surgery²⁶⁴.

Future AKI trials will probably use 'precision medicine' approaches that consider patient phenotype, endotype or both to maximize the potential for a beneficial response. In particular, the application of omics technologies, new imaging techniques, nanotherapeutics and digital health approaches may pave the way to the development of personalized and more effective therapies through a bench-to bedside approach. Omics technologies such as transcriptomics, proteomics, metabolomics, digitomics and epigenomics can be used to phenotype multiple types of biochemical sample and thereby to enable the discovery of biomarkers and therapeutic targets for AKI²⁶⁵. Advances in ultrasound technology based on microbubble properties and magnetic resonance imaging using manganese-based probes enable the evaluation of renal alterations during the early phases of AKI^{253,266–273}. Nanotherapeutics using selected nanomaterials or extracellular vesicles derived from various types of stem cell are emerging approaches that could limit the progression of CKD²⁷⁴. Last, the use of digital health solutions such as health information technologies, telehealth, mobile health applications, wearable devices and artificial intelligence could improve clinical care and outcomes¹⁸¹.

A broader approach is necessary to overcome the limitations in using therapeutic strategies across countries and different healthcare settings when managing AKI. Increasing population growth, ageing and the increased prevalence of hypertension, diabetes and obesity in LMICs will increase AKI episodes among a growing number of patients with reduced renal functional reserve. Environmental changes, including global warming, increased exposure to environmental toxins and air pollution, will worsen this scenario^{212,275}.

Randomized controlled trials have investigated various approaches for the prevention of AKI and progression to CKD that could potentially be adopted worldwide. For example, the PROTECTION trial, which enrolled 3,511 patients undergoing cardiac surgery in 22 centres in 3 countries, showed that infusion of a balanced mixture of L-amino acids was associated with a reduced incidence of AKI compared with placebo²⁷⁶. Whether the observed protective effect of amino acid infusion is simply due to recruitment of kidney function reserve that leads to a functional change, or whether the amino acids have protective effects on tubular cells, remains to be elucidated.

The DEFENDER trial, which enrolled 507 critically ill patients in 22 ICUs in Brazil, showed that addition of a sodium-glucose co-transporter 2 (SGLT2) inhibitor, dapagliflozin, to standard therapy did not significantly improve mortality (the primary outcome), need for dialysis, ICU-free days, hospital-free days, mechanical-ventilation-free days, KRT-free days, vasopressor-free days or organ dysfunction²⁷⁷. However, the researchers found a probability of benefit (0.9) of dapagliflozin for reduced need for KRT. This finding is in accordance with previous studies showing a potential protective effect of SGLT2 inhibitors on AKI development and progression. Other studies have suggested a protective effect of these drugs on senescence, a key cellular event involved in the triggering of fibrosis and AKI-to-CKD transition²⁷⁸.

Other RCTs evaluated commonly available drugs such as ascorbate and nicotinamide following promising findings in experimental and translational AKI studies. However, such efforts are hindered by a lack of appropriate experimental models of AKI that fully mimic the clinical setting. In one study, 30 patients enrolled within 24 h of diagnosis of septic shock were randomly assigned to receive a single mega-dose of sodium ascorbate or placebo²⁷⁹. Compared with placebo, sodium ascorbate induced a significant increase in urinary output and a greater reduction in vasopressor need and sequential organ failure assessment score, suggesting a possible protective effect on haemodynamics and kidney function. In a mouse model, low levels of the enzyme quinolinate phosphoribosyl transferase correlated with low kidney levels of nicotinamide adenine dinucleotide (NAD⁺) and the development of AKI²⁸⁰. A placebo-controlled phase-1 study in adults undergoing cardiac surgery showed that oral administration of nicotinamide resulted in an increase in circulating NAD⁺ metabolites and was associated with a lower incidence of AKI compared with placebo²⁸⁰.

Although these examples use drugs that can be administered at low cost and are often available in many, but not all, countries, they emphasize the current challenges in performing RCTs for AKI prevention and recovery because of the lack of evidence of significant benefit. Moreover, these studies underline the need for well-designed, prospective randomized controlled trials using specific enrichment strategies and subphenotyping of participants to limit AKI-related heterogeneities^{281,282}.

Conclusions

Almost a decade after the publication of the landmark Oby25 paper¹⁵, which characterized AKI as a “human rights case for nephrology”, the recognition, detection and management of AKI, particularly in LMICs, remains challenging. AKI contributes to short- and long-term adverse outcomes that constitute a substantial societal burden. Advances in knowledge of the epidemiology of AKI, aided by EHRs, digital health tools, point-of-care tests, improved communication capabilities (such as internet access), remote healthcare education and telehealth approaches, have aided in the identification of opportunities to improve care. At present, no specific treatments for AKI exist. However, several agents are in clinical trials, and the availability of kidney-injury-specific biomarkers and digital health technology for remote monitoring of patients has the potential to improve care. We must encourage initiatives and collaborations that promote awareness of AKI as a common, preventable and treatable disease through advocacy campaigns and continued publication of quality research that delineates the burden of AKI and tracks the outcomes of efforts to address this important global health issue.

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