Acute kidney injury—epidemiology, outcomes and economics

Oleksa Rewa and Sean M. Bagshaw

Abstract | Acute kidney injury (AKI) is a widespread problem of epidemic status. Compelling evidence indicates that the incidence of AKI is rapidly increasing, particularly among hospitalized patients with acute illness and those undergoing major surgery. This increase might be partially attributable to greater recognition of AKI, improved ascertainment in administrative data and greater sensitivity of consensus diagnostic and classification schemes. Other causes could be an ageing population, increasing incidences of cardiovascular disease, diabetes mellitus and chronic kidney disease (CKD), and an expanding characterization of modifiable risk factors, such as sepsis, administration of contrast media and exposure to nephrotoxins. The sequelae of AKI are severe and characterized by increased risk of short-term and long-term mortality, incident CKD and accelerated progression to end-stage renal disease. AKI-associated mortality is decreasing, but remains unacceptably high. Moreover, the absolute number of patients dying as a result of AKI is increasing as the incidence of the disorder increases, and few proven effective preventative or therapeutic interventions exist. Survivors of AKI, particularly those who remain on renal replacement therapy, often have reduced quality of life and consume substantially greater health-care resources than the general population as a result of longer hospitalizations, unplanned intensive care unit admissions and rehospitalizations.

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Introduction

Acute kidney injury (AKI, previously termed acute renal failure) is a common, increasingly encountered complication among patients hospitalized for acute illness.[1–3] The disorder is generally characterized by an abrupt deterioration in kidney function that disrupts metabolic, electrolyte and fluid homeostasis over a period of hours to days. The spectrum of AKI is broad, ranging from small changes in the levels of biochemical markers of kidney function to overt kidney failure requiring initiation of renal replacement therapy (RRT).

The clinical importance of AKI is exemplified by data showing a consistent association with increased long-term risk of poor outcomes, including death, incident chronic kidney disease (CKD), and greater utilization of health resources.[4] Compelling evidence from observational studies indicates that the incidence of AKI is increasing, and although mortality is concomitantly decreasing, more patients are ultimately suffering the long-term sequelae of AKI.[5,6] The reality is even more alarming considering the paucity of effective interventions to prevent AKI in at-risk patients or to mitigate established kidney damage, other than supportive measures, such as initiation of RRT.[7]

These observations strongly reinforce the global importance of increasing awareness of the poor outcomes and profound economic impact that AKI might have on patients, communities and health systems. In 2013, the World Kidney Day Steering Committee focused on AKI, directing awareness to its impact and calling for campaigns to promote the prevention and prompt identification of AKI in patients at risk as well as the implementation of evidence-informed protocols and policies to mitigate its impact.[8] In this Review we provide an overview of the evolving epidemiology, outcomes and economic implications of AKI.

Definitions of AKI

A wide array of operational definitions of AKI exists. For example, a systematic review of clinical studies focusing on cardiac surgery reported that >35 different definitions were used for AKI diagnosis.[9] This lack of standardization has created huge challenges for the optimal estimation of the burden of illness and outcomes attributable to the disorder (Figure 1). The RIFLE and AKIN consensus criteria were developed in response to the growing need for consistency and standardization in the diagnostic classification of AKI.[10–12] These classification schemes have since been combined in the KDIGO Clinical Practice Guideline for AKI.[13] The KDIGO AKI criteria use the conventional surrogates of kidney function, serum creatinine level and urine output, to define the presence and severity of kidney injury.[13] Numerous studies that evaluated these classification schemes (or their previous iterations) have shown gradient-response relationships between severity of AKI and risk of poor outcomes.[14]

Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Clinical Sciences Building, 2–124E, 8440–112 Street North West Edmonton, AB T6G 2B7, Canada (**O. Rewa**, **S. M. Bagshaw**).

Correspondence to: S. M. Bagshaw bagshaw@ualberta.ca

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Key points

- Acute kidney injury (AKI) occurs in an estimated one in five adults and one in three children hospitalized with acute illness; the incidence of AKI is increasing
- Subclinical AKI, defined as elevation in levels of kidney damage biomarkers not fulfilling the conventional criteria for AKI, has characterized a subgroup of patients with increased risk of poor outcome
- Bedside clinical information systems can enable real-time automated electronic alerting for patients at risk of AKI or who develop early AKI; these systems can be integrated with evidence-based decision support tools
- The mortality associated with AKI remains unacceptably high, and increasing severity correlates with increasing mortality, the highest of which is among patients with overt kidney failure requiring renal replacement therapy
- Reduced health-related quality of life and incident disability are increasingly recognized as important patient-centred outcomes following acute illness complicated by AKI
- AKI is now recognized as an important risk factor for nonrecovery of kidney function, incident chronic kidney disease, and accelerated progression to end-stage renal disease

Despite this new consensus on the definition of AKI, residual challenges relating to the classification schemes remain. For example, serum creatinine level as a surrogate biomarker of AKI has several well-recognized limitations. The RIFLE, AKIN and KDIGO classification schemes rely on a reference (baseline) serum creatinine measurement to calculate a relative change in serum creatinine level and stage the severity of AKI.[15,16] However, baseline serum creatinine levels are often unknown and their estimation (assuming an estimated glomerular filtration rate [eGFR] of 75 ml/min/1.73 m^2) might be inaccurate and associated with misclassification of AKI.[17–20] Moreover, serum creatinine level has a non-linear relationship with GFR and requires time to accumulate, contributing to delays in detection of important changes in kidney function.[21] Early detection of AKI is also dependent on how often serum creatinine is measured.[21] The generation of serum creatinine might be affected by baseline factors, pre-morbid illness (such as malnutrition and cirrhosis), drug interactions and acute illness (such as sepsis, major trauma or AKI).[22] Creatinine kinetics might be further modified by haemodilution as a result of fluid resuscitation and accumulation in acute illness.[23–25] Adjustment for fluid balance in critically ill patients at risk of AKI improves the diagnostic classification and identifies a previously 'unrecognized' subgroup of patients at higher risk of mortality compared to those without AKI.[23]

Numerous studies, in particular analyses of large observational datasets from administrative or registry databases, have omitted the urine output contribution in the definition of AKI. However, in the past few years, an association between episodes of oliguria and greater risks of worsening AKI, need for RRT and death has been confirmed.[26–29] Further data suggest that the current urine output threshold for the diagnosis of AKI (0.5 ml/kg/h for 6 h) is too sensitive and is not prognostically aligned with the serum creatinine criteria.[30] These findings have led to a call to lower the urine output threshold for AKI diagnosis to 0.3 ml/kg/h for 6 h to better correlate with worsening kidney function, need for RRT and death.[30]

The current classification schemes (RIFLE, AKIN and KDIGO) do not integrate novel kidney damage biomarkers (for example, neutrophil gelatinase associated lipocalin [NGAL], kidney injury molecule-1 [KIM-1], and interleukin-18 [IL-18]) for early diagnosis, severity staging and predicting prognosis of AKI.[31,32] Although these novel biomarkers have been reported to correlate with and predict worse outcomes of AKI, study findings are not consistent.[33–37] The concept of subclinical AKI has emerged from studies that characterized the association between kidney damage biomarkers and outcomes.[38,39] A subgroup of patients have been identified with elevated levels of these biomarkers (for example, NGAL) who do not fulfil the conventional consensus criteria for AKI but have increased risks of RRT initiation and death compared to those without elevation of these biomarkers.[35,40] However, the reported diagnostic performance of many of these biomarkers varies as a result of issues such as limitations in study design and methodology, differing patient populations, aetiology of AKI, timing of measurement relative to injury, specific factors related to individual biomarkers, and the selected thresholds for

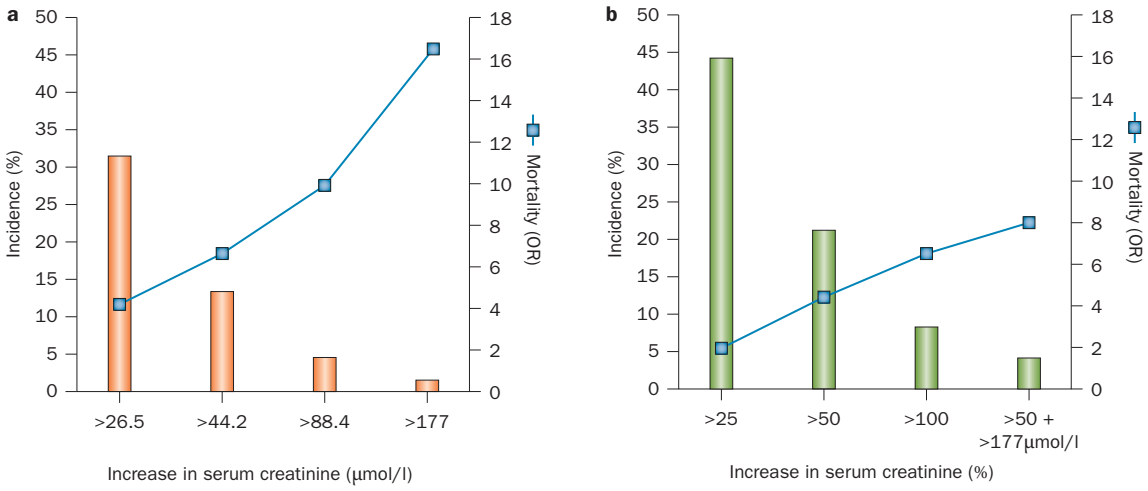

Figure 1 | Association between the incidence and mortality for acute kidney injury when assessed by **a** | absolute changes in serum creatinine levels and **b** | changes in serum creatinine levels relative to baseline. Data obtained from Chertow *et al.*[52]

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discriminating kidney damage and diagnosis of AKI.[31,32] This variability has generated challenges for their routine translation into clinical practice.

The development of consensus definitions for AKI was a monumental step towards improving the scientific understanding of the disorder. The role of these consensus definitions at the bedside to guide the clinical care of patients is still being evaluated and is not precisely defined.[41] Future refinement of the classification schemes is likely and is expected to involve investigation of modifications to the urine output criteria and the role of kidney damage biomarkers, integration of metrics of fluid balance and evaluation of time-averaged changes in serum creatinine levels.[42]

Hospitalized patients are increasingly monitored using electronic medical records and bedside clinical information systems. These systems can be automated to provide real-time electronic alerts to clinicians for patients considered to be at risk of AKI or who develop the diagnostic criteria for AKI. They can also be integrated with evidence-based decision support tools.[43] Use of such systems might provide a greater opportunity for clinicians to avoid or modify reversible risk factors (such as nephrotoxin exposure) compared with conventional recognition of AKI (that is, review of clinical data by a clinician during rounds).[41,43,44]

Epidemiology of AKI

Developed countries

A systematic review of 312 cohort studies, which included 49 million patients (mostly from high-income countries), found that AKI occurred in one in five adults and one in three children hospitalized with acute illness.[2] In a large US population (n = 3,787,410), the community-based incidence of nonRRT-requiring AKI (defined using relative changes in serum creatinine levels) and RRT-requiring AKI (defined using integrated administrative data) was estimated at 384.1 and 24.4 per 100,000 persons-years, respectively.[45] Between 1996 and 2003, the incidences of nonRRT-requiring and RRT-requiring AKI in this population increased significantly from 322.7 to 522.4 per 100,000 person-years (38%) and from 19.5 to 29.5 per 100,000 person-years (33%), respectively. The occurrence of AKI was most common among elderly, male and black patients. The observed incidence of non-RRT-requiring AKI in this study was much higher than prior estimates from studies that primarily used administrative claims data to ascertain AKI status; however, all of these studies reported significant increases in the incidence of AKI over time.[5,6,46,47] In a large retrospective cohort study (n = 49,518), approximately 1% of hospitalized patients had evidence of 'subacute' kidney injury, defined as relative changes in serum creatinine fulfilling the RIFLE classification for AKI but occurring over the duration of hospitalization rather than within 7 days.[48] Subacute kidney injury was independently associated with increased hospital mortality.

The use of administrative claims data for identifying AKI has shown poor sensitivity and might substantially underestimate the true incidence of AKI.[46,49,50] In a large Scottish cohort (n = 523,390), the population-based incidence of AKI, defined using the RIFLE criteria, was 1,811 per million population—considerably higher than previously thought.[51] Several plausible explanations for the growing secular trends in AKI incidence exist, including increased sensitivity of diagnostic coding in administrative data,[50] confounding by 'coding creep'[6] (that is, increased use of administrative codes for AKI) and increased sensitivity of consensus diagnostic criteria.[51] However, the available evidence strongly suggest that the true incidence of AKI is growing. These observations are reinforced by data showing that sensitive definitions of AKI incorporating small relative changes in serum creatinine levels correspond to marked increased risks of poor outcomes.[52,53]

In the USA, the incidence of hospital-acquired AKI increased from 4.9% in 1979 to 7.2% in 1996.[54,55] In a large Australian single-centre, hospital-based cohort study (n = 20,126), the incidence of AKI (defined using RIFLE criteria) was 18% and worsening RIFLE category correlated with near-linear increases in mortality.[56] Similar secular trends have also been noted for severe AKI requiring RRT. For example, a US study that used data from the Nationwide Inpatient Sample dataset reported a 10% annual increase in the incidence of AKI requiring RRT from 222 cases per million-person years in 2000 to 533 cases per million-person years in 2009.[57] In a population-based study in Ontario, Canada, which included 552,672 patients, the incidence of RRT utilization after elective surgery increased significantly from 0.2% in 1995 to 0.6% in 2009.[58] This increase was the result of increased utilization of RRT after cardiac and major vascular surgeries.

Several large cohort studies have focused on describing the incidence of AKI in intensive care settings.[16,59–70] In a large multinational study, the incidence of AKI among patients admitted to intensive care units (ICUs) was only 5.7%.[68] However, this study used a definition of AKI (that is, urine output <200 ml in 12 h; serum urea >30 mmol/l or initiation of RRT) that was intended to identify only those patients who were most severely affected (of whom approximately 70% required RRT). Subsequent cohort studies that integrated consensus definitions of AKI and used administrative databases reported AKI incidences in the ICU setting of 16–39%;[61,67] however, these studies often omitted or modified urine output criteria, used estimated reference serum creatinine levels or ascertained AKI status within 24 h of ICU admission. Two large cohort studies of critically ill patients described incidence rates of AKI of 65–67%.[64,69] The marked increased incidence in these studies is likely attributable to application of consensus AKI criteria as intended, with inclusion of the urine output criteria.[10,11,13] The population-based incidence of RRT utilization among critically ill patients with AKI is 11–19 cases per 100,000, which represents 4–8% of all critically ill patients.[15,68,70,71] Similar to population and hospital-based studies, secular trends of growing AKI incidence in ICU settings have been described. In a cohort that included more than 90,000 patients admitted to ICUs in 20 centres across Australia and New Zealand over a 10-year period,

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Box 1 | Risk factors for AKI

Non-modifiable
- Old age[15,16,46,55,82,93,95]
- Male sex[46,93]
- Black race[46,95]
- Pre-existing chronic kidney disease[46,55,63,91–93,95,96]
- Proteinuria or elevated albumin-to-creatinine ratio[87,89]
- Hypertension[93]
- Diabetes mellitus[93,95]
- Chronic liver disease and/or complications of portal hypertension[16,93,95,96]
- Heart failure and/or decreased ejection fraction[16,46,93,95,96,203]
- Coronary artery disease and/or recent myocardial infarction[95,204]
- Chronic obstructive pulmonary disease[46,93,95,96]
- Peripheral vascular disease[93]
- Malignancy[16]

Potentially modifiable
- Anaemia[149]
- Critical illness[23,46,56]
- Sepsis[16,46,51,65,117,120,205,206]
- Trauma[46,137,207]
- Cardiac surgery[94,95,115]
- Major noncardiac surgery[68,93]
- Exposure to radiocontrast media[110]
- Fluid overload[128,129,131,152,208,209]
- Fluid resuscitation with synthetic colloids (hydroxyethyl starch)[63,121–123,210,211] or chloride rich solutions (0.9% saline)[125,126,212]
- Drug toxicity, drug interactions or nephrotoxic medications[98,100–105,108,213]
- High-risk or emergency procedures[93–96]

the incidence of AKI increased by 2.8% per year, whereas associated mortality decreased by 3.4% per year.[60]

Developing countries

Although a substantial majority of data on the epidemiology of AKI are from developed countries,[2] AKI is increasingly recognized as an important contributor to morbidity, mortality and economic loss worldwide, particularly in developing countries.[8] One of the challenges associated with estimating the epidemiology of AKI in developing regions is that the available data are often from small, single-centre studies with low methodological quality and limited generalizability. However, these contributions still provide important indications of the broader burden of AKI and serve to focus attention on the disorder.

In general, AKI might be more likely to occur in children and healthy adults in developing countries than in developed countries because of a host of socioeconomic and environmental influences.[72] Factors contributing to AKI such as infectious diseases (that is, tropical febrile illnesses such as diarrhoea, leptospirosis, malaria and dengue fever), envenoming (as a result of snake, spider or insect bites and/or stings), and obstetrical complications are described far more commonly in studies from developing countries than in those from developed countries.[73–79] Importantly, in large metropolitan regions in developing countries, the clinical profile of patients at risk of AKI, or in whom AKI occurs, might be very similar to that encountered in developed countries.[75,80] Failure to measure kidney function among patients at increased risk of AKI is associated with a missed opportunity to intervene and mitigate worsening kidney function and also contributes to gross underestimation of the scope of the problem in developing countries.[81] These observations further reinforce the importance of initiatives to raise awareness of AKI, such as those promoted by World Kidney Day in 2013.[8]

Factors associated with AKI

Extremes of age

A wide array of patient-specific and context-specific factors can modify the risk of AKI. Elderly and very young patients are particularly susceptible to the disorder. Although older age has consistently been shown to increase the risk of AKI,[15,16,45,82,83] elderly patients with AKI are far less likely to receive RRT than are younger patients.[45,84,85] Hospitalized children are also at increased risk; up to 50% of acutely ill children develop AKI, most commonly in association with major surgery and/or sepsis.[86]

Proteinuria

Pre-existing proteinuria is a risk factor for development of AKI among hospitalized patients.[87] In patients with proteinuria and eGFR >60 ml/min/1.73 m^2, the adjusted risk of AKI was 4.4-fold higher than in those with no proteinura.[87] A similar increased risk of AKI associated with elevated urine albumin-to-creatinine ratio was further increased by declining eGFR.[88] In a large cohort of patients undergoing cardiac surgery, increased urine albumin-to-creatinine ratio independently predicted post-operative AKI (as defined by the AKIN classification) and improved clinical risk prediction. Abnormally elevated urine albumin-to-creatinine ratio was also associated with increased dialysis risk, mortality and prolonged ICU and hospital stays.[89]

Comorbid diseases

Overt CKD is a recognized risk factor for death, cardiovascular events and hospitalizations[90] and is also an independent risk factor for development of AKI, nonrecovery of renal function and progression to end-stage renal disease (ESRD).[91,92] CKD is one of the strongest predictors of AKI, as evidenced by its integration into numerous clinical practice guidelines and risk prediction scores for development of post-procedural AKI and need for RRT.[93–97] Nonrenal comorbid diseases also modify the risk of AKI.[15,16] Diabetes mellitus, hypertension, cardiovascular disease (that is, coronary artery disease and heart failure), peripheral vascular disease, chronic liver disease (that is, cirrhosis and portal hypertension), and chronic obstructive pulmonary disease have been implicated as important risk factors for development of AKI (Box 1).[93–97]

Exposure to nephrotoxins

Population-based studies have shown an increased risk of hospitalization-requiring AKI following initiation

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Table 1 | Studies evaluating the association between selected medications and risk of AKI

Study	Design	Population (*n*)	Medications	Definition of AKI	Outcome
Dormuth *et al.*[100]	Multicentre, nested, case-controlled	Ambulatory, aged ≥40 years, new statin users (2,067,639)	High potency statins	Diagnostic codes	AKI in patients without CKD: RR 1.34 (95% CI 1.25–1.43) AKI in patients with CKD: RR 1.10 (95% CI 0.99–1.23)
Leonard *et al.*[101]	Nested, case-controlled	Ambulatory (1,351,832)	Proton pump inhibitors	Diagnostic codes	Acute interstitial nephritis: adjusted OR 3.2 (95% CI 0.8–12.8) AKI: adjusted OR 1.05 (95% CI 0.97–1.14)
Schneider *et al.*[98]	Nested, case-controlled	Mixed hospital, aged >65 years (121,722)	Nonsteroidal anti-inflammatories (including cyclooxygenase 2 inhibitors)	ICD-9-CM within 30 days of treatment initiation	AKI: adjusted RR 2.1 (95% CI 1.6–2.6)
Wikman *et al.*[103]	Prospective cohort	Ambulatory, HIV positive (271)	Highly active antiretroviral therapy	RIFLE criteria	Incidence of AKI 10% (7 cases per 100 patient years)
Sorli *et al.*[102]	Single-centre, prospective cohort	Mixed ICU (102)	CMS	RIFLE criteria	Incidence of AKI 25.5% at 7 days; 49.0% at end of treatment ↑ Trough CMS plasma levels associated with ↑ risk of AKI
Bird *et al.*[99]	Nested, retrospective cohort	Mixed hospital, males aged 40–85 years (13,943)	Fluoroquinolones (current use)	ICD-9-CM	Fluoroquinolones alone: RR of AKI 2.2 (95% CI 1.7–2.7) Fluoroquinolones plus renin–angiotensin system blockers: RR of AKI 4.5 (95% CI 2.8–7.0)
Zappitelli *et al.*[106]	Single-centre, retrospective cohort	Hospitalized children not in the ICU (557)	Aminoglycosides	Paediatric RIFLE criteria	Incidence of AKI 33% AKI associated with ↑ length of hospital stay and health-care costs
Zhao *et al.*[104]	Multicentre, retrospective cohort	Ambulatory, aged >66 years, new fibrate user (19,072)	Fibrate	Diagnostic coding	↑ SCr: adjusted OR 2.4 (95% CI 1.7–3.3) Nephrologist consultation: adjusted OR 1.3 (95% 1.0–1.6) No ↑ risk of dialysis-requiring AKI
Ramirez *et al.*[108]	Single-centre, prospective chort	Mixed hospital (179)	Vancomycin	RIFLE criteria	↑ Trough levels of serum vancomycin and other nephrotoxins associated with ↑ risk of AKI
Centers for Disease Control and Prevention[214]	Case series	Ambulatory (16)	Synthetic cannabinoids	Not specified	Clustered cases, recent use associated with AKI and need for renal replacement therapy
Radaelli *et al.*[213]	Single-centre, retrospective cohort	Cardiac surgery (3,139)	Angiotensin-converting-enzyme inhibitors	Increase in SCr level of 50% or 44 μmol/l in hospital	AKI: OR 1.23 (95% CI 1.01–1.73)

Abbreviations: AKI, acute kidney injury; CMS, colistin methanesulfonate sodium; ICD-9-CM, International Classification of Diseases—9th Revision—Clinical Modification; ICU, intensive care unit; OR, odds ratio; RIFLE, risk, injury, failure, loss, end-stage renal disease; RR, relative risk; SCr, serum creatinine.

of or exposure to commonly prescribed medications, including high potency statins, proton pump inhibitors, non-steroidal anti-inflammatory drugs, fluoroquinolones, fibrates and highly active anti-retroviral therapy (Table 1).[98–104] Similarly, AKI is increasingly associated with adverse drug interactions, toxicity, inappropriate prescriptions, failure of clinicians to adjust for kidney function when calculating dosages in at-risk patients, and continued exposure to nephrotoxins during AKI.[105,106] Worsening AKI and hypotension are the most common, potentially avoidable, adverse drug reactions, with angiotensin-converting-enzyme inhibitors and antithrombotics commonly implicated.[105] Hospitalized patients, particularly those in ICUs, are often exposed to multiple concurrent nephrotoxins.[102,103,107–109] Antimicrobials are common sources of avoidable nephrotoxicity[55,68,99,102,106,108,109] and exposure to contrast media is also frequently associated with AKI in hospitalized patients.[55] In a single-centre study of critically ill patients admitted to ICU who underwent contrast-enhanced radiography examination, contrast-induced AKI developed in 16.3% of the 787 participants and was associated with higher use of RRT and significantly increased 28-day mortality (adjusted OR 2.7, 95% CI 1.4–5.5).[110]

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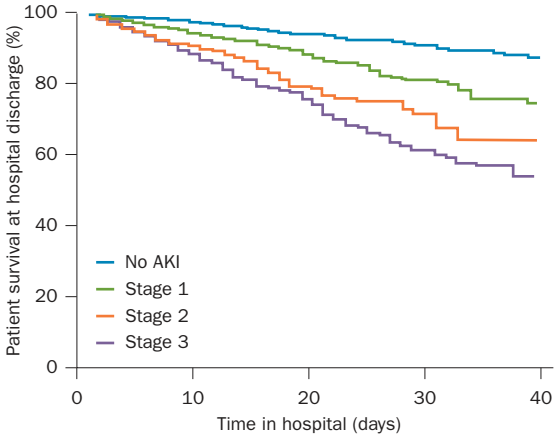

Figure 2 | Kaplan–Meier graph for hospital survival, stratified by KDIGO stages of acute kidney injury. Reproduced with permission from Oxford University Press © Wang, H. E. *et al.* Comparison of absolute serum creatinine changes versus Kidney Disease: Improving Global Outcomes consensus definitions for characterizing stages of acute kidney injury. *Nephrol. Dial. Transplant.* **28**, 1447–1454 (2013).

Major surgery

AKI after major non-cardiac surgery is uncommon; however, its incidence is modified by the burden of baseline susceptibilities and perioperative factors.[111] In a prospective, single-centre cohort of patients undergoing major non-cardiac surgery ($n = 15{,}102$), AKI (defined as creatinine clearance <50 ml/min in the first 7 days after surgery) occurred in 0.8% of participants and was associated with increased mortality at 30 days, 60 days and 1 year.[111] Perioperative risk factors included older age, higher BMI, comorbid disease, and high-risk or emergency surgeries. In addition, perioperative modifiers included total vasopressor dose, use of vasopressor infusion and diuretic infusion. Among those patients who required temporary support in ICU after surgery, AKI occurred in 9.6% and resulted in prolonged ICU and hospital stays and higher mortality. In a study that used a US database of 152,244 operative procedures to derive and validate a clinical risk score for AKI (defined as a serum creatinine level >177 μmol/l or need for RRT within 30 days of surgery), AKI occurred in 1% of patients and increasing clinical risk score correlated with greater risk of AKI. Patients who had more than five risk factors had a 9% incidence of AKI and a significantly increased risk of 30-day mortality.[93]

The estimated incidence of AKI (defined using RIFLE or KDIGO criteria or as a 50% increase in serum creatinine levels from baseline) in patients undergoing cardiac surgery is 11–30%.[112–115] Severe AKI requiring RRT occurs in an estimated 1–2% of these patients.[116] Numerous studies have derived clinical risk scores of predictors of AKI after cardiac surgery (Box 1).[94] The strongest predictors of post-operative AKI among clinical risk scores are baseline kidney function and CKD status.[95,96] Patients with decreases in serum creatinine levels from baseline immediately after surgery were less likely to develop AKI compared to those whose serum creatinine levels increased after surgery.[112]

Sepsis

In ICUs, AKI occurs most commonly in association with sepsis and is associated with a marked increase in risk of adverse outcomes.[62,64,68,117,118] A multicentre cohort study found that 64.4% of critically ill patients with septic shock ($n = 4{,}532$) developed AKI within 24 h of ICU admission.[119] Delay in administration of appropriate antimicrobial therapy after the onset of hypotension was associated with increased risk of AKI. In a multicentre cohort of 33,375 patients admitted to ICUs with a sepsis-related diagnosis, 42.1% had early AKI as defined by the RIFLE criteria.[117] Sepsis is a known precipitating factor for AKI and the development of AKI further predisposes to episodes of sepsis.[120] Higher RRT use and risk of death has been reported in patients with sepsis occurring after AKI compared with patients without sepsis.[120]

Fluid resuscitation and overload

Randomized trials of fluid resuscitation using the synthetic colloid hydroxyethyl starch compared with crystalloids have shown higher risk of AKI and RRT use, in particular in patients with sepsis.[121–123] Administration of chloride-rich solutions (that is, 0.9% saline) compared with balanced crystalloid solutions are also associated with increased risk of AKI and greater use of RRT in surgical and critically ill patients.[124–126] Chloride loading might result in deleterious changes in renal haemodynamics and contribute to excess fluid retention.[127]

Fluid overload is increasingly associated with AKI.[23,128,129] Numerous mechanisms might contribute to the adverse renal consequences of fluid overload, including increased systemic venous pressure, renal-specific parenchymal oedema, intra-abdominal hypertension, and the physiological impact of interventions to treat fluid overload (that is, mechanical ventilation and diuretic therapy). Fluid overload in critically ill patients with AKI has consistently been associated with increased mortality in observational studies.[129–131]

Outcomes of AKI

Mortality

The risk of mortality associated with AKI is unequivocal and consistent across numerous clinical contexts, including acute myocardial infarction,[132–134] acute decompensated heart failure,[135] major non-cardiac[93,136] and cardiac surgeries,[53] and critical illness.[61,67–69,71] Despite secular trends in demographic transition characterized by an ageing population, greater prevalence of comorbid illness, higher illness severity and higher intensity of support, AKI-associated mortality is decreasing.[2,5,6,60] However, this mortality remains unacceptably high. The estimated unadjusted mortality associated with an episode of AKI was recently estimated at 23.9% in adults and 13.8% in children.[2]

Increasing severity of AKI correlates with increasing mortality, which is highest in patients with overt kidney failure requiring RRT (Figure 2).[15,56,61,68,69,71] The adjusted risk of in-hospital mortality shows near linear increases with worsening severity of AKI[56] and this relationship

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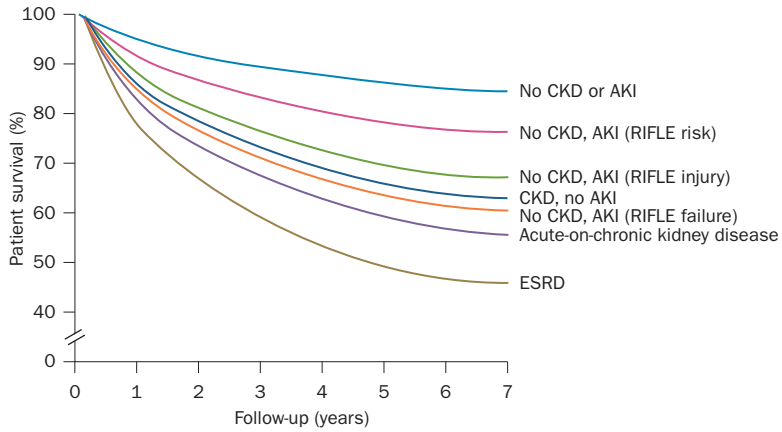

Figure 3 | Long-term survival stratified by CKD and AKI. Cox proportional hazard model for long-term survival of patients alive at hospital discharge, stratified by severity of AKI for patients without CKD (no AKI and RIFLE risk, injury, and failure groups) and by occurrence of AKI for patients with CKD (no AKI and acute-on-chronic kidney disease groups). Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; RIFLE, risk, injury, failure, loss, end-stage renal disease. Reproduced with permission from Nature Publishing Group © Wu, V. C. *et al. Kidney Int.* **80**, 1222–1230 (2011).

is universally evident across specific settings, such as contrast-induced nephropathy, cardiac surgery, major trauma, sepsis and critical illness.[67,69,70,115,137] A multicentre, population-based cohort study of 2,901 patients with nonRRT-requiring AKI (defined according to RIFLE criteria) in Finnish ICUs reported in-hospital and 90-day mortality of 25.6% and 33.7%, respectively.[63] Patients who survive an acute hospitalization associated with AKI remain at excess increased risk of mortality long after the inciting event compared with those without AKI.[138–140] Among US patients who survived for at least 90 days after discharge from an acute-care hospitalization ($n = 864{,}933$), long-term mortality was 29.8% in those with AKI compared with only 16.1% in those who did not have AKI (adjusted relative risk 1.41, 95% CI 1.39–1.43).[138] Similarly, in a Canadian population-based cohort of critically ill patients with AKI who did not require dialysis ($n = 41{,}327$), the risk of long-term mortality was increased compared with a matched cohort of critically ill patients without AKI (adjusted hazard ratio 1.10; 95% CI 1.07-1.13).[139]

AKI-associated mortality is highest among patients with severe AKI requiring RRT, particularly in the setting of critical illness, with estimated in-hospital mortality approaching 60%.[15,68,141] Emerging data, however, suggest that the mortality of patients with AKI is decreasing.[6,71,142] In hospital, 90-day and 6-month mortality among patients with AKI treated with RRT have been reported as 35%, 45% and 49%, respectively.[63,142]

The factors that contribute to AKI-associated mortality vary with time and differ in the immediate and long-term. Factors that modify the risk of early mortality occurring in-hospital or less than 90 days after AKI include the primary diagnosis (such as sepsis), severity of acute illness and the burden of acute nonrenal organ dysfunction.[70] Among early survivors, factors contributing to intermediate and long-term mortality include older age, pre-existing comorbid disease (CKD, cardiovascular disease or malignancy) and incomplete organ recovery with ongoing residual disease.[140] Although large epidemiological surveys have described the mortality associated with AKI, relatively little insight has been available on the proximate causes of death among patients with AKI. In a cohort study of 3,930 hospitalized patients prospectively identified as having AKI (according to the AKIN criteria), in-hospital mortality was 21.9% and data on the primary cause of death was available for 93.4% of the deceased patients.[143] Death was primarily attributed to sepsis (41.1%), cardiovascular events (19.2%) and malignancies (12.9%), whereas AKI was listed as the primary cause of death in only 3.1% of patients.

Recovery of kidney function

Nonrecovery of kidney function following an episode of AKI is a major morbid event with long-term implications for patients and health resources. No consensus on a definition of renal recovery after AKI exists; however, the majority of studies have defined renal nonrecovery as dialysis dependence. In large observational cohort studies of critically ill patients with severe AKI requiring RRT, the rate of dialysis dependence at hospital discharge was 13–29%.[15,68,144–146] Among survivors of AKI, the rate of dialysis dependence seems to decrease at 6 months and 12 months after AKI onset; however, this result is often confounded by deaths that occur predominantly among those patients who remain on dialysis.[15,141]

Several patient-level susceptibilities modify the likelihood of nonrecovery from AKI and rapid progression to ESRD, in particular older age[147] and severity of CKD at baseline (Figure 3).[140,148] Both the severity of AKI and the number of AKI episodes are associated with the development of incident CKD and ESRD.[149,150] Hospitalized patients might be exposed to multiple, potentially avoidable inciting events during their illness that might worsen AKI and reduce the probability of recovery.[102,103,105,107,108] Although no validated scoring systems that reliably predict recovery of kidney function after AKI are currently available, data from studies that integrated novel biomarkers of kidney damage (that is, NGAL) into models for clinical risk prediction are promising.[151]

Fluid accumulation is associated with misclassification and delayed diagnosis of AKI[23,24] and several studies have shown that fluid accumulation and overload independently predict mortality in patients with AKI.[129–131,152] Moreover, fluid overload at the time of initiation of RRT has been associated with nonrecovery of kidney function.[153] These data suggest that a metric of fluid overload should be considered an important trigger for initiation of RRT, and might be more relevant for clinical decision support than serum creatinine levels alone. In addition, a systematic review suggested that delayed initiation of RRT in critically ill patients with AKI is associated with a non-significant increase in kidney nonrecovery.[153] Further high-quality randomized trials to investigate this issue are expected.[154,155] The impact of the initial RRT modality in critically ill patients with AKI on recovery

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Table 2 | Selected studies evaluating the impact of initial RRT modality on renal recovery after AKI

Study	Location	Year(s) of enrolment	Design	Population (*n*)	Definition of renal recovery	Outcome (CRRT versus IRRT)
Mehta *et al.*[159]	USA	1991–1995	Multicentre, randomized clinical trial	Mixed ICU (166)	SCr ≤177 μmol/l (2 mg/dl)	↑ Complete recovery with CRRT
Bell *et al.*[144]	Sweden	1995–2004	Multicentre, retrospective cohort	Mixed ICU (2,642)	RRT-free	↓ ESRD with CRRT (8% versus 17%)
Uchino *et al.*[161]	Worldwide	2000–2001	Multicentre, prospective cohort	Mixed ICU (1,218)	RRT-free	↓ Dialysis dependence with CRRT (11% versus 35%)
Jacka *et al.*[157]	Canada	2004	Multicentre, retrospective cohort	Mixed ICU (116)	RRT-free	↓ Dialysis dependence with CRRT (17% versus 64%)
Lin *et al.*[158]	Taiwan	2002–2006	Multicentre, prospective cohort	Surgical ICU (342)	RRT-free	↑ Recovery with CRRT
Cartin-Ceba *et al.*[156]	USA	2003–2006	Multicentre, retrospective cohort	Mixed ICU (11,664)	NA	↑ ESRD with IRRT
Andrikos *et al.*[59]	Greece	2008	Multicentre, prospective cohort	Mixed ICU (170)	RRT-free	↓ Dialysis dependence with CRRT (15% versus 25%)
Wald *et al.*[162]	Canada	1996–2009	Multicentre, retrospective cohort, ≥90 day survival after initiation of RRT	Mixed ICU (4,008)	RRT-free	↓ ESRD with CRRT (16% versus 26%)

Abbreviations: CRRT, continuous RRT; ESRD, end-stage renal disease; ICU, intensive care unit; IRRT, intermittent RRT; NA, not applicable; RRT, renal replacement therapy; SCr, serum creatinine.

of kidney function is an area of renewed interest.[141,142] Initial renal support with continuous RRT (CRRT), compared with intermittent RRT is associated with a higher likelihood of recovery to dialysis independence (Table 2).[141,144,156–162]

Few data are available on the long-term risk of incident CKD and progression to ESRD in patients with less-severe forms of AKI. The risk of incident ESRD is reported to be 2.7-fold higher among critically ill patients with AKI who do not require RRT than among patients without AKI.[139] These patients are also at increased risk of major cardiovascular events, rehospitalization and mortality.[139,163] However, following an episode of AKI, early as opposed to late recovery to baseline kidney function is associated with a lower risk of adverse events and long-term mortality.[114,164]

Health-related quality of life and disability

Health-related quality of life (HRQL) and residual disability are increasingly recognized as important patient-centred outcomes following acute illness complicated by AKI.[165] A number of studies have described HRQL for patients with AKI associated with critical illness (Table 3).[71,136,166–171] The majority of these studies are fairly small, single-centre and primarily focused on functional disability and HRQL among survivors of severe AKI requiring RRT. In general, HRQL is lower at hospital discharge and at 6 months after AKI onset in survivors of AKI compared with the age and sex-matched general population. Older age, greater comorbid disease, higher illness severity, longer durations of ICU and hospital stays, and dialysis dependence are associated with significantly lower HRQL.[169,171] At 6 months after initiation of RRT, the physical components of HRQL in patients with AKI were generally more affected than the mental components,[167] but better cognitive function was reported in the dialysis-independent survivors.[169] Poor HRQL has been shown to predict mortality in survivors of AKI at 1 year.[170] However, despite lower perceived HRQL compared with an age and sex-matched general population, many survivors of AKI requiring RRT report that their HRQL is acceptable and they would choose to receive the same treatment course again.[167]

Few studies have evaluated HRQL following AKI not requiring RRT.[136,168] Despite lower baseline HRQL and greater disability compared with a matched general population, survivors of AKI not requiring RRT showed improvements in HRQL at 6 months to levels commensurate with survivors of critical illness without AKI.[168]

Economics of AKI

Resource implications of AKI

The development of AKI in hospitalized patients increases direct and indirect health-care costs and resource utilization across a broad range of conditions.[52] AKI is associated with greater investigations and monitoring, unplanned or longer ICU stays, prolonged hospitalization and an increased risk of early rehospitalization. In a US study,[52] hospitalized patients who developed KDIGO stage 2 AKI had a reported 6.5-fold increased adjusted odds ratio for death, a prolonged hospital stay (>3.5 days), and an additional USD$9,000 in hospital costs compared with hospitalized patients who did not develop AKI.[52]

Uncomplicated AKI, defined as AKI not in association with critical illness, contributes an excess $2,600 in attributable costs and a median of five additional days of hospitalization.[172] These direct hospital costs exceed those of several more-prevalent conditions including hospitalizations for heart failure ($2,200), pneumonia ($2,100) and gastrointestinal bleeding ($2,100).[52]

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Table 3 | Studies evaluating HRQL among survivors of AKI

Study	Location	Years of enrolment	Design	Population (*n*)	Instrument	Outcome
Korkeila *et al.*[145]	Finland	1992–1993	Single-centre, retrospective cohort	Mixed ICU, requiring RRT (3,447)	NHP and ADL	↓ HRQL, reduced energy and limited physical mobility at 6 months after AKI
Ahlstrom *et al.*[166]	Finland	1998–2002	Single-centre, prospective cohort	Mixed ICU, requiring RRT (153)	EQ-5D	↓ HRQL and quality-adjusted survival in patients on RRT compared with age and sex-matched general population
Johansen *et al.*[169]	USA	2003–2007	Substudy of randomized controlled trial	Mixed ICU, requiring RRT (415)	HUI	Poor HRQL Longer ICU and hospital stays and dialysis dependence associated with worse HRQOL
Joyce *et al.*[170]	USA	2003–2007	Substudy of randomized controlled trial	Mixed ICU, requiring RRT (439)	HUI	HRQL poor and associated with ↑ risk of 1-year mortality
Morsch *et al.*[171]	Brazil	2006–2008	Single-centre, prospective cohort	Mixed ICU, requiring RRT (68)	SF-36	↑ HRQL at 6 months associated with younger age, fewer comorbidities, less-severe illness, no sepsis and shorter ICU stay
Abelha *et al.*[136]	Portugal	2006–2008	Single-centre, retrospective cohort	Surgical, AKI according to AKIN criteria (50)	SF-36 and ADL	↓ HRQL and ↑ ADL at 6 months in patients with AKI compared with those without AKI
Delannoy *et al.*[167]	France	2007–2008	Multicentre, prospective cohort	Mixed ICU, requiring RRT (77)	SF-36 and ADL	↓ but acceptable HRQL in survivors of AKI compared with the general population Improved HRQOL of AKI survivors 1–6 months after AKI; physical components more severely affected than mental components
Vaara *et al.*[71]	Finland	2007–2008	Multicentre, retrospective cohort	Mixed ICU, requiring RRT (1,686)	EQ-5D	At 6 months, HRQL was similar for survivors of AKI on RRT and those who did not require RRT
Hofhuis *et al.*[168]	Netherlands	2000–2007	Single-centre, prospective cohort	Mixed ICU, AKI according to RIFLE criteria (398)	SF-36 (by proxy)	↓ HRQL at baseline and at 6-month follow-up in survivors of AKI compared with the general population ↓ HRQL at discharge in AKI survivors but no difference at 6 months compared with patients without AKI

Abbreviations: ADL, activities of daily living; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; EQ-5D, EuroQOL; HRQL, health-related quality of life; HUI, health utilities index; ICU, intensive care unit; NHP, Nottingham Health Profile; RIFLE, risk, injury, failure, loss, end-stage renal disease; RRT, renal replacement therapy; SF-36, short form 36.

The development of AKI in critically ill patients contributes to prolonged mechanical ventilation, failed weaning from mechanical ventilation, greater use of tracheostomy and longer ICU stays.[173,174] In patients who develop AKI after cardiac surgery, the attributable cost and utilization of RRT increases with the severity of injury.[175] Patients with KDIGO stage 1 AKI after cardiac surgery had a 1.6-fold longer duration of ICU stay and a 1.6-fold increase in total post-operative costs compared with those who did not develop AKI.[175] Moreover, hospitalized patients with AKI who did not require RRT had higher rates of rehospitalization (adjusted hazard ratio 1.21, 95% CI, 1.18-1.24) compared to those without AKI.[139]

Resource implications of acute RRT

The initiation of RRT in patients with severe AKI represents a measurable increase in the complexity of care and associated costs. The application of RRT across different centres is variable and is associated with differences in adjusted mortality.[176] However, adjusted mortality might be lower in larger centres that perform a higher annual volume of treatments than in smaller centres.[177]

Haemodialysis

The daily cost of CRRT is more than that of intermittent haemodialysis.[178–182] In an analysis of data from 53 centres in 23 countries, the median cost of CRRT per treatment day was $290 more expensive than that of intermittent haemodialysis; however, the median cost differences were highly variable across centres (the median daily cost of CRRT compared with intermittent haemodialysis ranged from $3,630 excess to $379 less).[181] The greatest costs attributable to CRRT are for replacement and dialysate fluids and the extracorporeal circuit. In a Canadian retrospective cohort study that evaluated the immediate and long-term costs of RRT modalities, the weekly cost of daily CRRT ranged from $3,283 to $4,819 (depending on the specific therapy and anticoagulant used) compared with only $1,263 for three times weekly intermittent haemodialysis.[179] The direct costs of any RRT are predominantly attributable to

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human resources (such as dialysis nurses), extracorporeal circuits and filters, replacement and dialysate fluids and anticoagulants.

The costs associated with replacement and dialysis fluids for CRRT might be modestly reduced by ensuring a dose-delivery of 25 ml/kg/h or timely transition to intermittent haemodialysis when physiologically appropriate for the patient.[181] In-hospital and 1-year direct health-care costs are lower among AKI survivors with renal recovery ($44,921 and $10,541, respectively) than among those who remain on dialysis ($52,778 and $69,011, respectively).[179] Higher rates of renal recovery and dialysis independence have been reported among survivors of AKI whose initial therapy was CRRT compared with those who initially received intermittent haemodialysis, suggesting that the continuous therapy might prove to be cost-effective in the long-term.[144,160–162] The role of hybrid RRTs, such as slow low-efficiency dialysis, is still being defined.[183]

Peritoneal dialysis

In many regions of the world, peritoneal dialysis is a more commonly used renal replacement modality in patients with severe AKI than is CRRT or intermittent haemodialysis.[184,185] A randomized trial that included 70 critically ill adults with septic AKI, reported that CRRT compared with peritoneal dialysis was associated with faster resolution of azotemic and metabolic complications, higher survival, and lower relative costs per life saved (that is, greater cost effectiveness).[185] However, a number of potential methodological concerns regarding this trial have cast doubt on these findings.[186,187] A systematic review of 24 studies, which included 1,556 patients with AKI, compared outcomes of peritoneal dialysis with those of other forms of extracorporeal blood purification and found no statistically significant difference in mortality despite the overall low methodological quality of the included studies.[184] Subsequent studies have suggested that high volume continuous peritoneal dialysis using an automated cycler in patients with AKI can achieve reasonable azotemic, metabolic and fluid balance control with a low rate of complications.[188–190] Indeed, peritoneal dialysis is an important RRT modality in developing regions where it might not only be cost-effective relative to CRRT, but might be the only option available.[191] Additional high quality studies are needed to increase our understanding of the role of peritoneal dialysis in AKI.

Long-term cost-effectiveness of RRT

Few studies have evaluated the cost-effectiveness of RRT in critically ill patients with AKI beyond the immediate direct costs.[145] In the SUPPORT study, the estimated cost per quality-adjusted life-year (QALY) saved for critically ill patients with AKI started on RRT (compared with withholding support and allowing death to occur) was $128,200.[165] In this study, which had a follow-up duration of 4.4 years, median patient survival was 32 days and only 27% of patients were alive at 5 months. Even among those patients deemed most likely to survive, the cost per QALY saved was high at $61,900. In a Finnish cohort of 410 critically ill patients with AKI treated with RRT, the overall cost per QALY saved during 5-year follow up was poor (>$339,729) and was excessive in older patients (>$1,358,904).[192] However, from a societal perspective, the costs were more acceptable in those patients who survived for >1 year (<$67,945 per QALY saved). In both of these studies the outcomes among survivors of AKI were reasonably good as defined by the patients; however, the cost of RRT far exceeded the commonly cited $50,000 per QALY saved threshold for cost-effective care.

Incident CKD and progression to ESRD

AKI is an independent risk for incident CKD and progression to ESRD,[139,149,163,193] with predictable implications for health-care costs at the patient and societal level. The attributable annual costs of CKD to the Medicare programme have been estimated as minimal for stage 1 CKD, $1,700 for stage 2 CKD, $2,500 for stage 3 CKD and $12,700 for stage 4 CKD,[194] whereas the annual attributable costs of ESRD, although variable by RRT modality, average approximately $52,236.[195] ESRD is responsible for approximately 1.2% of total health care expenditure in Canada[195] and 1–2% of the total National Health Service budget in the UK.[196] In the USA, costs are more difficult to estimate but data from the US Renal Data System suggest that ESRD accounts for approximately 6.7% of all Medicare expenditure.[197] Incident CKD and progression to ESRD among children and adults carries a considerable individual and societal burden. CKD is associated with higher risk of hospitalizations, cardiovascular events and mortality[90] along with reduced HRQL and impaired physical function.[198,199]

The long-term economic implications for children surviving an episode of AKI are particularly relevant.[86,200] In a small cohort study of critically ill children with AKI ($n = 226$) in New Zealand, the majority of patients survived but 40% had persistent abnormalities (for example, hypertension, abnormal urinalysis) at hospital discharge, suggesting ongoing kidney injury.[86] In a Canadian 3-year follow-up study of critically ill children with AKI ($n = 126$), 10% of survivors had evidence of CKD with a higher incidence in those with more-severe AKI.[200] A relative paucity of longer-term epidemiological evaluations of kidney health among children surviving an episode of AKI exists. Among children and adolescents, the long-term sequelae and the economic impact of AKI progression to CKD are potentially devastating and might include reduced HRQL, depression, social isolation and education and employment constraints.[201,202] Further studies are needed to quantify the full economic and social implications of CKD and ESRD among children and adults following an episode of AKI, including the number of productive years lost and the effects on life expectancy, ability to enter the workforce and use of social assistance.

Conclusions

AKI is a problem of epidemic proportions and likely deserves similar attention as other common medical

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problems encountered in acute care medicine, such as acute myocardial infarction and stroke, which are associated with similar risks of adverse outcomes. Abundant data confirm that the incidence of AKI, particularly in hospitalized patients, is rising. This increasing incidence is largely attributable to a higher prevalence of susceptibilities and heightened exposure to potentially modifiable risks during hospitalization. AKI is associated with an increased risk of adverse outcomes, including short-term and long-term mortality, incident CKD, accelerated progression to ESRD and reduced HRQL, and also contributes to excess consumption of healthcare resources. The downstream economic impact of AKI might be profound, particularly among survivors who fail to recover kidney function and remain dialysis dependent.

Future research will be directed at improving these poor outcomes associated with AKI by focusing on: improved calibration in the diagnostic criteria for AKI to enable early and reliable identification of those patients who are most at-risk of AKI (for example, understanding the role of novel kidney damage biomarkers and fluid balance); evaluation of the impact of adherence to current KDIGO clinical practice guidelines for better identification and management of patients with AKI; evaluation of novel therapeutics aimed at reducing the incidence of AKI and/or mitigating the development of maladaptive repair during recovery from AKI to reduce the incidence of incident or worsening CKD; and better understanding the optimal application of acute RRT in those developing worsening or severe AKI (that is, when to ideally start and discontinue and the ideal RRT modality to use for selected circumstances).

Review criteria

A search for original articles published between 1980 and 2013 and focusing on acute kidney injury was performed in MEDLINE and PubMed. The search terms used were "acute kidney injury OR acute renal failure", "renal replacement therapy OR continuous OR intermittent OR peritoneal", "epidemiology OR incidence", "mortality", "renal recovery AND chronic kidney disease OR end stage renal disease", "quality of life", "economic OR cost effectiveness OR quality-adjusted life year", alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

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Both authors researched the data for the article, contributed to discussions of the content, wrote the article and reviewed and edited the manuscript before submission.

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