CKJ REVIEW

Long-term consequences of acute kidney injury: a narrative review

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ABSTRACT

The incidence of acute kidney injury (AKI) has increased in the past decades. AKI complicates up to 15% of hospitalizations and can reach up to 50–60% in critically ill patients. Besides the short-term impact of AKI in patient outcomes, several studies report the association between AKI and adverse long-term outcomes, such as recurrent AKI episodes in 25–30% of cases, hospital re-admissions in up to 40% of patients, an increased risk of cardiovascular events, an increased risk of progression of chronic kidney disease (CKD) after AKI and a significantly increased long-term mortality. Despite the long-term impact of AKI, there are neither established guidelines on the follow-up care of AKI patients, nor treatment strategies to reduce the incidence of sequelae after AKI. Only a minority of patients have been referred to nephrology post-discharge care, despite the evidence of improved outcomes associated with nephrology referral by addressing cardiovascular risk and risk of progression to CKD. Indeed, AKI survivors should have specialized nephrology follow-up to assess kidney function after AKI, perform medication reconciliation, educate patients on nephrotoxic avoidance and implement strategies to prevent CKD progression. The authors provide a comprehensive review of the transition from AKI to CKD, analyse the current evidence on the long-term outcomes of AKI and describe predisposing risk factors, highlight the importance of follow-up care in these patients and describe the current therapeutic strategies which are being investigated on their impact in improving patient outcomes.

Keywords: AKI, cardiovascular, CKD, mortality, outcomes

INTRODUCTION

Acute kidney injury (AKI) is an acute decrease in kidney function defined by an increase in serum creatinine (SCr) or a decrease in urine output (UO) [1, 2]. The incidence of AKI has increased in the past decades, reflecting the increased recognition of this diagnosis, patient ageing and increase in AKI risk factors and co-morbidities [diabetes, hypertension, chronic kidney disease (CKD), cardiovascular disease (CVD), liver disease, lung disease, sepsis and surgery] and exposure to nephrotoxic drugs [1, 3–7]. AKI complicates 5.0 to 15.0% of hospitalizations and can reach up to 50–60% in critical care patients [1, 3–7]. Despite remaining significantly high, mortality rates have declined in the past decade reflecting improvements in patient care, namely by improvements in dialytic care, availability of less nephrotoxic drugs and a decrease in use of dopamine and diuretics [2, 7–9].

The increase in survival of AKI patients, has contributed to a significant increase in long-term outcomes associated with AKI, namely recurrence of AKI episodes, development or progression of CKD, characterized by the presence of kidney disease for >90 days, increasing risk of cardiovascular events, increasing

hospital admissions, reduced quality of life and long-term mortality [10–15] (Figure 1).

Despite the long-term impact of AKI, there are neither established guidelines on the follow-up care of AKI patients, nor treatment strategies to reduce the incidence of sequelae after AKI. Indeed, only a minority of patients received comprehensive nephrology post-discharge care, despite the evidence of improved outcomes associated with nephrology referral by addressing cardiovascular risk and risk of progression to CKD [16, 17].

The authors provide a comprehensive review of current evidence of the long-term outcomes of AKI and predisposing risk factors, and highlight the importance of follow-up care in improving patient outcomes.

MATERIALS AND METHODS

We conducted two literature searches in May 2020, using MEDLINE through the PubMed search engine with the MeSH terms: (i) AKI, prognosis and (ii) AKI, long term, outcomes.

We included articles published in English after the year 2010 up to 20 May 2020, of adult patients with AKI measuring mortality, dialysis dependence, CKD and cardiovascular events.

Diagnosis and pathophysiology of AKI

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines define AKI as an increase in SCr of at least 0.3 mg/dL within 48 h, or an increase in SCr >1.5 times baseline within the prior 7 days, or a decrease in UO to <0.5 mL/kg/h for 6 h [18]. This classification further stratifies AKI according to three stages of disease severity which correlate with worse degrees of prognosis [18] (Figure 2).

The kidney is highly susceptible to systemic imbalances and the causes of AKI range from pre-renal AKI, acute tubular necrosis, acute interstitial nephritis, acute glomerular diseases and acute obstructive nephropathy [19]. The most common causes of AKI in hospitalized patients are septic shock, post major surgery, cardiogenic shock and hypovolaemia [20].

The pathophysiology of AKI is a complex interplay of pathways triggered by an inciting event which leads to an imbalance of oxygen supply and demand [21–25]. These processes include haemodynamic instability, microcirculatory dysfunction, tubular cell injury, tubular obstruction, renal congestion, microvascular thrombi, endothelial dysfunction and inflammation [21–26].

Despite affecting all the segments of the nephron, proximal tubular cells are the most frequently injured, causing loss of polarity, apoptosis or necrosis, which depend on severity of injury [26, 27]. Damage to proximal tubular cells consequently results in afferent arteriolar vasoconstriction mediated by tubuloglomerular feedback, luminal obstruction and back leak of filtrate across injured proximal tubular cells, which leads to an abrupt decrease in glomerular filtration [21]. Additionally, kidney injury prompts the production and release of inflammatory and vasoactive mediators causing leucocyte adherence and interstitial infiltration and lead to microcirculatory flow disruption.

Indeed, inflammation is considered to play a critical role in the pathophysiology of AKI, namely in local kidney injury, in the multi-organ failure associated with AKI, in kidney recovery and also in the progression to CKD which can result if these immune mechanisms persist [26–30].
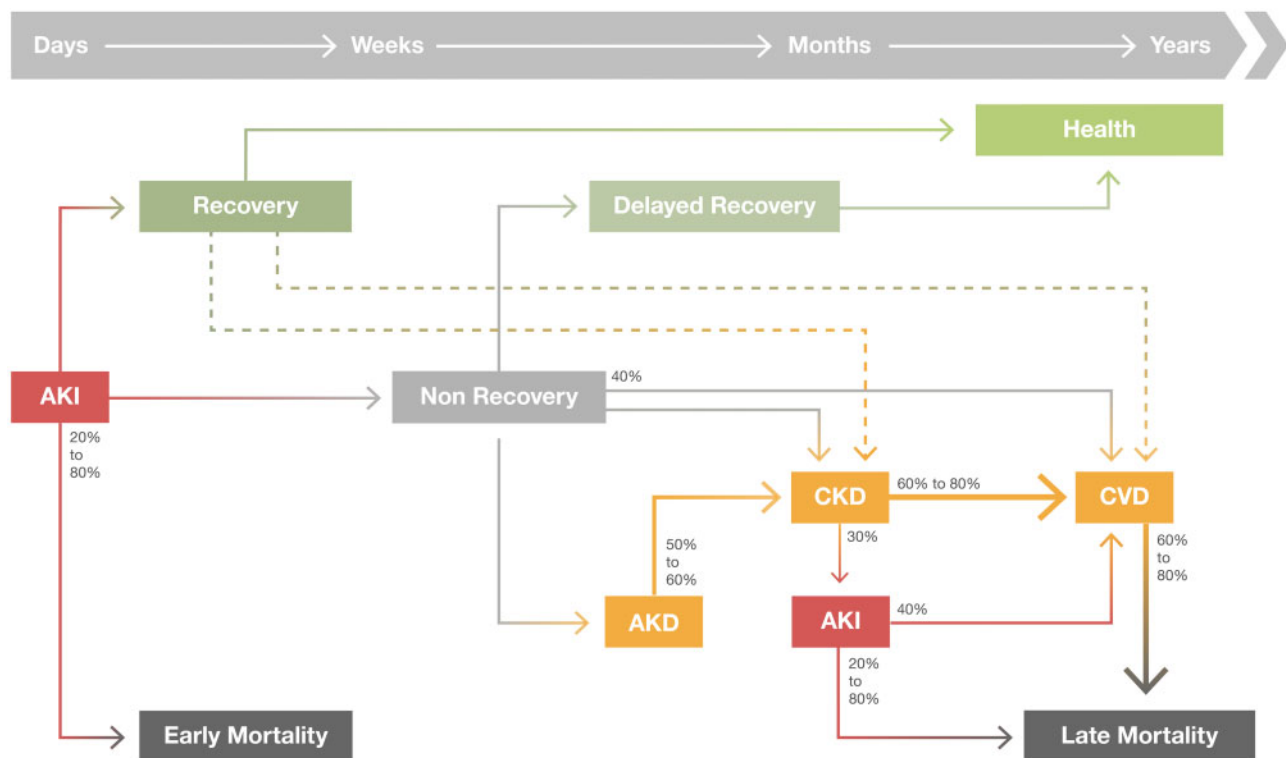
FIGURE 1: Long-term consequences after AKI. An AKI event can lead to renal recovery or development of Acute kidney disease (AKD). In the long-term, AKI and AKD are associated with development or progression of CKD, recurrent AKI episodes, risk of cardiovascular events and higher risk of long-term mortality. Even AKI recovery has been associated with increased long-term outcomes.
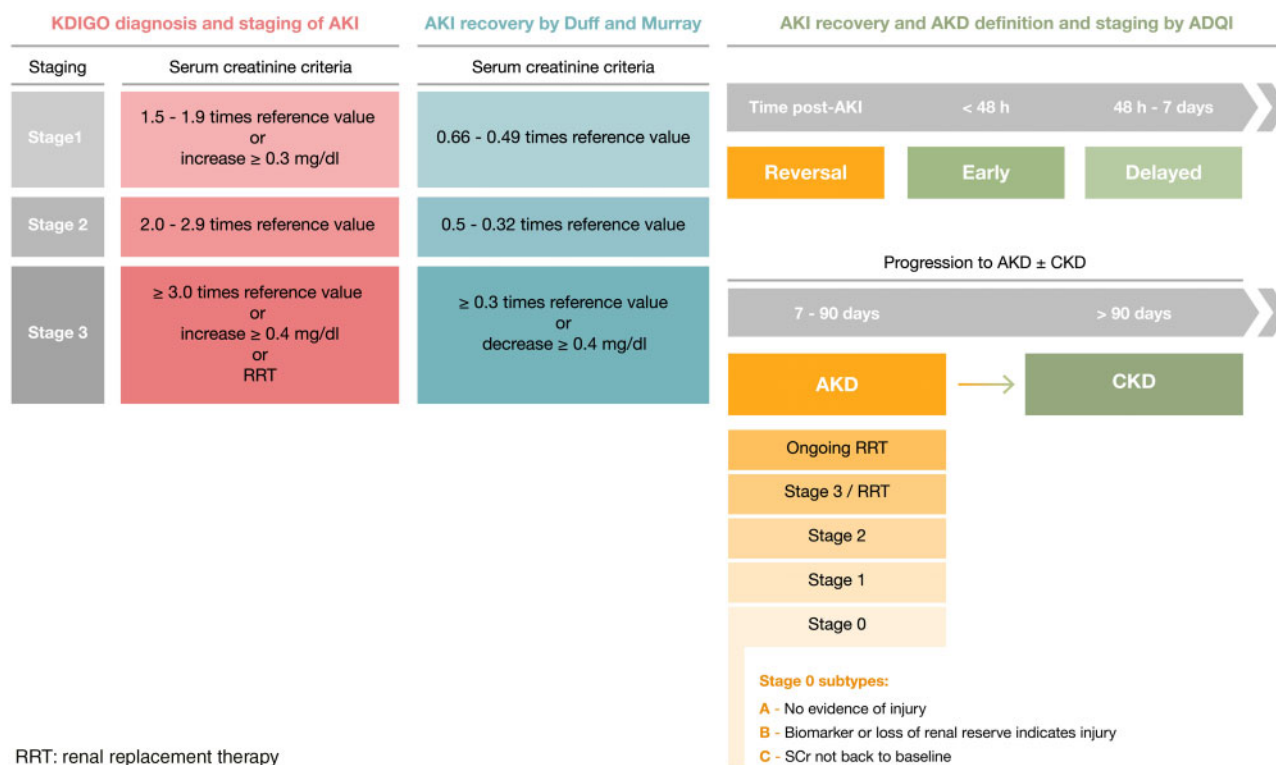
FIGURE 2: AKI, AKI recovery and AKD definitions (adapted from KDIGO, Acute Disease Quality Initiative (ADQI) and from Duff and Murray [56]).

TIME COURSE OF AKI

It is postulated that transient AKI reflects a temporary reduction in renal function without structural damage, whereas persistent AKI reflects structural tubular damage [31–34]. The duration of AKI could also reflect the potential to recover the injured kidney [31, 33, 35]. Additionally, the degree of severity of the patient's illness can also impact on AKI duration [31, 33]. Thus, non-recovery from AKI seems to be predisposed by several mechanisms resulting in the exposure of a reduced nephron mass to higher injury in association with impaired repair mechanisms [36].

Several studies have reported an association of rapid recovery of kidney function and better short-term survival [37–42]. Coca et al. conducted the largest prospective study to date demonstrating the prognostic impact of AKI duration [31]. In their cohort of postoperative AKI diabetic patients, the mortality rate increased by AKI duration when stratified by AKIN stage [31]. They demonstrated that the mortality rate for patients with AKIN Stage 1 with a duration of >7 days was >2-fold higher than for patients with AKIN Stage 3 for <2 days [31] (Figure 3).

The previous classifications systems of AKI do not take into account the duration of AKI, which is a significant aspect of AKI severity [37]. The Acute Disease Quality Initiative (ADQI) has recently defined transient AKI when baseline kidney function is recovered within 48 h, while persistent AKI is defined as kidney dysfunction which persists for longer than 48 h (Figure 2) [37].

AKI recovery

Renal recovery after AKI is a complex process which is not entirely understood though appears to be dependent on AKI severity, aetiology, duration and baseline renal function [43]. The timeline and trajectory of renal recovery will depend on reversal of the pathophysiological processes involved [44]. Renal repair may be the result of regeneration of cells and reestablishment of polarity [27].

Studies report that the incidence of renal recovery can range from 0% to 90% considering all stages of AKI severity, but from 0% to 40% in cases of dialysis requiring AKI [36]. The heterogeneity in populations studied and in AKI and reversibility definitions used has contributed to the difficulty in defining and quantifying renal recovery after AKI [36]. The most often used criteria to assess renal recovery is a decrease in SCr, which is associated with certain limitations, such as loss of muscle mass, changes in volume of distribution, changes in renal reserve and hyperfiltration [45]. This is supported by studies demonstrating the increased risk in CKD after AKI even when there is an apparent return of SCr to baseline [46, 47].

The presence of proteinuria has also been recognized as a marker of underlying kidney injury and has been associated with worse outcomes after AKI episodes [48]. Novel biomarkers for AKI are being researched to more accurately assess renal recovery, namely plasma neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor metalloproteinase-2 and insulin-like growth factor binding protein-7 ([TIMP-2] $\times$ [IGFBP7]), urine concentrations of interleukin (IL)-18 and liver-type fatty acid-binding protein (L-FABP) [49–52].

The ideal definition of kidney recovery after AKI should accurately assess baseline kidney function to differentiate non-recovery from pre-existing CKD, current residual kidney function and reserve and be able to provide prognosis.

The trajectory of renal recovery can take many forms and is associated with long-term prognosis [36]. Recovery can be assessed as a relative or absolute change, or as a fixed threshold, and according to how persistent an episode of AKI is or to how sustained the recovery is [53]. Kellum et al. identified five

phenotypes of renal recovery after AKI, namely early sustained AKI reversibility, late sustained AKI reversibility, relapse AKI and recovery, relapse AKI without recovery and never recovered AKI, which had distinct characteristics and correlated differently with prognosis [54]. In this study, non-recovery of renal function at hospital discharge was frequent and associated with an increase risk in mortality (Figure 4). Interestingly, late recovery of renal function was associated with better outcomes than non-recovery, and worse than early reversal of renal function [54]. Heung *et al.* also identified different patterns of renal recovery after AKI and reported an increasing risk of CKD according to AKI severity, duration of injury and time to recovery and that this risk was significant even in mildest forms of AKI with fast recovery [47]. Therefore, outcomes are not only associated with the degree of renal recovery but also with time to recovery.

In 2017, the ADQI defined AKI reversal as the absence of AKI by both SCr and UO criteria (according to the KDIGO classification) within 7 days after the AKI inciting event. The term acute kidney disease (AKD) was thus proposed to define a condition in which AKI Stage 1 or greater (KDIGO) is present for a duration between 7 and 90 days after AKI onset [55]. Thus, AKD follows on from AKI in patients who do not fully recover within 7 days and is stratified in four different stages of severity (Table 1).

A recent perspective by Duff and Murray reflects on the lack of standardized definition of renal recovery in the literature and proposes that AKI recovery could be defined as a decrease of SCr of at least 33% from the reference SCr (value at admission or value which led to AKI diagnosis) within 7 days [56]. They also categorize AKI recovery into three stages inversely correlated with the KDIGO SCr criteria [56]. This approach would increase
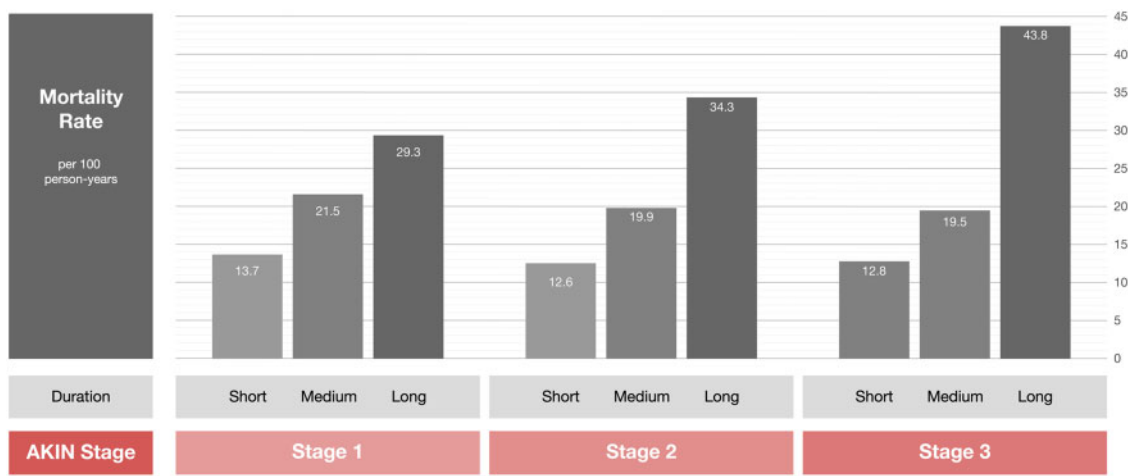
FIGURE 3: Impact of AKI severity and duration on mortality (adapted from Coca *et al.* [31]).
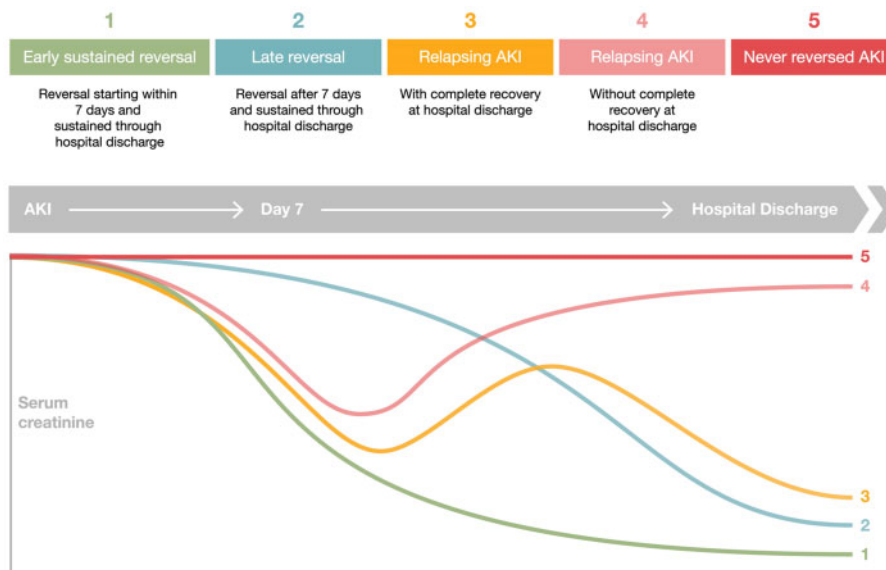
FIGURE 4: Time course of AKI (adapted from Kellum *et al.* [54]). Patients who develop AKI may experience (i) early sustained reversal of AKI (reversal before 7 days and sustained till hospital discharge), (ii) late reversal (reversal after 7 days and sustained till hospital discharge), (iii) relapsing AKI with complete recovery at hospital discharge, (iv) relapsing AKI without complete recovery at hospital discharge and (v) non-reversal of AKI.

the recognition of AKI recovery and allow to assess its impact on long-term outcomes.

Important factors associated with non-recovery post-AKI include older age, presence of co-morbidities such as CKD, hypertension, diabetes mellitus and CVD, higher severity of the acute illness reflected by higher Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) or Simplified Acute Physiology Score (SAPS) scores, haemodynamic instability, medical admission, higher severity of AKI, requirement of renal replacement therapy (RRT) and potentially the intermittent modality of RRT, though this remains controversial [36, 54, 57–60] (Figure 5). Hence, non-recovery after AKI results from the exposure of a relatively decreased nephron mass or with impaired repair mechanisms to greater injury.

Pathophysiology of AKI to CKD transition. Under certain circumstances, the pro-fibrotic and pro-inflammatory pathways can result in maladaptive repair and transition to CKD after AKI [44]. Older age, lower baseline kidney function, longer duration of AKI and higher severity of AKI contribute to maladaptive repair [44]. Thus, severe and repeated injury superimposed on reduced renal reserve in an inflammatory environment can result in a maladaptive repair, characterized by a permanent reduction in kidney function associated with significant structural changes resulting from a complex interaction of injured renal tubular cells, endothelial cells, renin–angiotensin–aldosterone system (RAAS), immune system and interstitial fibroblasts [61, 62].

Persistent inflammation and RAAS activation are crucial mechanisms in AKI to CKD transition [62, 63]. Indeed, studies have demonstrated an association between RAAS inhibition and lower risk of CKD progression, though no randomized controlled trials have been performed with this goal [64]. The mechanisms of CKD progression after AKI include nephron loss and consequent hypertrophy of the remaining nephrons which leads to further tubulointerstitial fibrosis and further nephron loss; interstitial immune cell infiltration which leads to interstitial fibrosis; peritubular capillary loss resulting in renal hypoxia accelerating inflammation and fibrosis; injured renal tubular cells can adopt a profibrotic phenotype after cell cycle arrest, affecting other epithelial cells, pericytes and the immune system;

Table 1. AKD Classification according to the ADQI

Stages	AKD (7–90 days after AKI event)
0	A: Absence of criteria for B or C
	B: Continued evidence of ongoing injury, repair and/or regeneration or indicators of loss of renal glomerular or tubular reserve
	C: SCr < 1.5 times baseline but not back to baseline levels
1	SCr = 1.5–1.9× baseline
2	SCr = 2–2.9× baseline
3	SCr = 3× baseline
	SCr ≥ 4 mg/L
	Ongoing need for renal replacement therapy

AKI	AKI non-recovery	Development and progression of CKD	Cardiovascular outcomes	Long-term mortality
Older Age	Older Age	Older Age	Older Age	Older Age
Hypertension	Hypertension	Hypertension	Hypertension	Hypertension
CKD	CKD	CKD	CKD	CKD
CVD	CVD	CVD	CVD	CVD
Diabetes	Diabetes	Diabetes	Diabetes	Diabetes
	Severity of AKI	Severity of AKI	Severity of AKI	Severity of AKI
Hypoalbuminemia		Hypoalbuminemia		Hypoalbuminemia
Anemia		Anemia		
		Duration of AKI		Duration of AKI
		Female gender		Male gender
		Illness severity		Illness severity

Others

Liver disease	Black Race	AKI relapses		Cancer
Lung disease	Hemodynamic instability	Albuminuria		AKI recovery
HIV infection	Medical admission	Need for RRT		
Obesity	RRT modality	Timing and type of AKI recovery		
Shock				
Sepsis				
Nephrotoxins				
Surgery				
Hyperuricemia				
Hyperglicemia				

FIGURE 5: Risk factors associated with AKI and outcomes post-AKI.

and maladaptive repair which promotes the activation and growth of fibroblasts which contribute to the deposition of extracellular matrix and resulting fibrosis [44, 61, 65, 66].

The term AKD reflects the continuing pathological processes and adverse events developing after AKI, highlights the importance of renal recovery and reinforces the hypothesis that AKI and CKD are a continuum rather than separate entities [55].

Biomarkers of AKI to CKD transition. Biomarkers of these pathological processes, such as epithelial tubular injury, cell cycle arrest, systemic inflammatory pathways and glomerular filtration, would help identify patients at risk for CKD development [44]. Elevated levels of urinary and serum kidney injury molecule 1 (KIM-1), NGAL, L-FABP, IL-18 and TIMP-2 × IGFBP7 indicate persistent tubular injury, which could be used to identify risk of later CKD development [44, 48, 67, 68]. Indeed, in 692 patients, TIMP-2 × IGFBP7 > 2.0 at admission was associated with mortality or dialysis at 9 months (hazard ratio (HR) = 2.16, 95% CI 1.32–3.53) [69]. Also, urinary angiotensinogen has been associated with higher AKI severity and mortality and considering the role of RAAS activation in progression to CKD is considered a promising prognostic marker [44, 70]. Further investigations on anti-fibrotic interventions are required to develop strategies to preserve renal function and prevent the transition from AKI to CKD.

Long-term renal outcomes

Recent research described the association between AKI and long-term renal outcomes such as recurrent AKI episodes, development and progression to CKD. In recent systematic reviews, the pooled rate of CKD after AKI ranged from 10.17 to 25.8 cases per 100 person-years [71, 72].

Recurrent AKI. AKI has been associated with increased rates of hospital readmissions. The rate of readmission increases with AKI severity and can reach up to 40% in AKI requiring dialysis within the first month [73–76].

Several studies have focused on the incidence of recurrent episodes of AKI (Table 2). Liu *et al.* conducted one of the largest studies on AKI, including 38 659 patients with hospital-acquired AKI and identified a second AKI episode in 28.6% of patients [77]. Furthermore, recurrent AKI was associated with an increased mortality risk (HR = 1.66; 95% CI 1.57–1.77). Likewise, Siew *et al.* reported recurrent AKI in 25% cases in a population of 11 683 patients [78]. Furthermore, the 1-year mortality was higher in patients with recurrent AKI (35% versus 18%, P < 0.001) [78].

In a large population of hospitalized and community patients, Holmes *et al.* identified a recurrence rate of AKI of 30% and an association of recurrent AKI and higher 30-day mortality rate (OR = 1.33, 95% CI 1.28–1.38) [79]. Interestingly, with each episode of AKI, the probability of another episode also increased [79].

This has also been proven in intensive care unit (ICU) patients. Harris *et al.* demonstrated that AKI was associated with recurrent AKI episodes (OR = 1.9, 95% CI 1.0–3.6) in a cohort of 624 critically ill surgical patients. Moreover, recurrent AKI was associated with increased 1-year mortality (OR = 2.6, 95% CI 1.4–5.1) [80]. An increasing mortality risk associated with recurrent AKI was also demonstrated in a study of 400 critically ill septic patients in which the incidence of AKI was 20% (HR = 1.97, 95% CI 1.36–2.84) [81].

Table 2. Summary of studies assessing AKI and AKI recurrence

References	Design	Setting	N	AKI definition	Incidence (%)	Recurrent AKI (%)	CKD	Mortality
Liu et al. [77]	Retrospective	Hospitalized patients	429 852	KDIGO	9	28.6		Recurrent AKI = HR = 1.66, 95% CI 1.56–1.77
Siew et al. [78]	Retrospective	Hospitalized patients	11 683	KDIGO	100	25		
Holmes et al. [79]	Case series	Hospitalized and community patients	111 528	KDIGO	100	29.3		Recurrent AKI = OR = 1.38, P < 0.001
Harris et al. [80]	Retrospective	Non-cardiac surgery ICU patients	624	RIFLE	47	31		Recurrent AKI = OR = 1.2, 95% CI 1.1–1.3
Rodrigo et al. [81]	Prospective	ICU septic patients	400	KDIGO	82.8	19.8		Recurrent AKI = HR = 1.97, 95% CI 1.36–2.84
Thakar et al. [82]	Prospective	Diabetic patients	3679	AKIN	70	30	13.6% HR =3.56, 95% CI 2.76–4.61	
Rodriguez et al. [4]	Retrospective	Hospitalized patients	359	ADQI	100	34	HR = 2.2, 95% CI 1.09–4.3, P = 0.003	

Table 3. Summary of studies assessing AKI and long-term outcomes

References	Design	Setting	N	AKI definition	Incidence (%)	CKD	CVD	Mortality	Follow-up, years
Wald et al. [84]	Retrospective case-match	Hospitalized patients	3769–13.598	AKI requiring dialysis		HR = 3.26, 95% CI 2.73–3.89		HR = 0.95, 95% CI 0.89–1.02	5
Goldberg et al. [85]	Prospective	STEMI patients	1957	RIFLE	17.7			Persistent mild AKI: HR = 2.3, 95% CI 1.4–3.7, P < 0.001 Transient moderate/severe AKI: HR = 2.0, 95% CI 1.2–3.2, P < 0.004 Persistent moderate/severe AKI: HR = 2.7, 95% CI 1.5–4.6, P < 0.001	3
Wu et al. [86]	Observational	Surgical CKD patients	9425	RIFLE	46.6			HR = 2.62, 95% CI 1.92–3.57, P < 0.001	5
Schiffl et al. [87]	Prospective	ICU patients	425	AKI requiring dialysis	100			1 year 65%5-year 75%10-year 80%	10
Pannu et al. [88]	Observational	Hospitalized patients	190 714	KDIGO	3.7	AKI non-recovery HR = 4.13, 95% CI 3.38–5.04		AKI non-recovery HR = 1.26, 95% CI 1.10–1.43	6
Fuchs et al. [89]	Retrospective	Critical care patients	12 399	AKIN	54.3			AKIN 1: HR = 1.26, 95% CI 1.14–1.40, P < 0.001 AKIN 2: HR = 1.28, 95% CI 1.11–1.47, P = 0.001 AKIN 3: HR = 1.61, 95% CI 1.30–1.99, P < 0.001	2
Horne et al. [90]	Prospective case control	Hospitalized patients	300	AKIN	50	14% versus 0.7%, P < 0.001			1
Chawla et al. [61]	Retrospective	Hospitalized patients	36 980	KDIGO	22.8	HR = 2.07, 95% CI 1.99–2.16	AKI + MI: HR = 1.24, 95% CI 1.18–1.30	HR = 1.85, 95% CI 1.76–1.94	1
Ryden et al. [91]	Retrospective	Cardiac surgery patients	29 330	AKIN	13	HR = 6.24 (1.94–20.1)		AKIN 1: 1.34, 95% CI 1.23–1.45 AKIN 2/3: 2.32, 95% CI 2.01–2.68	6
Wu et al. [92]	Case-control	Hospitalized patients	4869–4869	AKI requiring dialysis	50		HR = 1.67, 95% CI 1.36–2.04, P < 0.001	HR = 1.67, P < 0.001	3
Rimes-Stigare et al. [93]	Retrospective	ICU patients	97 782	KDIGO	5.4	6.0% versus 0.44%, IRR 7.6%		61.8% versus 39.1%	5
Xu et al. [94]	Prospective	Cardiac surgery patients	3245	KDIGO	39.9	HR = 20.32, 95% CI 4.55–97.31, P < 0.001		HR = 1.74, 95% CI 1.27–2.37, P < 0.001	2
Hansen et al. [95]	Observational	Cardiac surgery patients	4742	KDIGO	30.7		HR 1.41, 95% CI 1.11–1.80	HR = 1.37, 95% CI 1.05–1.80	5
Heung et al. [47]	Retrospective	Hospitalized patients	104 764	KDIGO	16.3	31.8% (AKI) versus 15.5% (no AKI), P = 0.001			1
Gameiro et al. [96]	Retrospective	Abdominal surgery patients	390	KDIGO	18.5	47.2% versus 22.0%; HR 1.65, 95%		44% versus 19.8%; HR = 1.4, 95% CI 1.10–2.00, P = 0.043	4

(continued)

Table 3. (continued)

References	Design	Setting	N	AKI definition	Incidence (%)	CKD	CVD	Mortality	Follow-up, years
Soliman et al. [97]	Retrospective	Critical care pateints	2420	RIFLE	34.4	CI 1.01–2.50, P = 0.046		Injury: HR = 1.35, 95% CI 1.10–1.65, P = 0.004; Failure: HR = 1.77, 95% CI 1.37–2.28, P < 0.001	1
Parikh et al. [98]	Prospective	Cardiac surgery patients	968	AKIN	36		HR 1.99, 95% CI 1.46–2.71		4
Ferreiro et al. [99]	Retrospective	Cardiac surgery patients	7075	KDIGO	36.1			Mortality in 3.5 years: HR = 1.330, 95% CI 1.123–1.750	15
Kofman et al. [100]	Retrospective	STEMI patients	225	KDIGO	100			AKD: HR = 2.42, 95% CI 1.52–3.92, P < 0.001	4
Arias-Cabrales et al. [101]	Retrospective	Hospitalized patients	360	ADQI	100	6.5%		CKD: OR = 1.03,95% CI 1.03–1.06, P < 0.05	4
Pourafkari et al. [102]	Prospective	Non-cardiac surgery patients	7564	AKIN	8.5	OR = 34.95, 95% CI 20.88–58.52, P < 0.001	OR = 6.37, 95% CI 5.27–7.70, P < 0.001	OR = 2.26, 95% CI 1.97–2.60, P < 0.001	15
Lee et al. [103]	Observational	Cardiac surgery patients	45 108	AKI requiring dialysis	2.8	HR = 15.59, 95% CI 13.89–18.33, P < 0.001	HR = 1.97, 95% CI 1.75–2.23, P < 0.001	HR = 2.72, 95% CI 2.44–3.02, P < 0.001	3
Mizota et al. [104]	Retrospective	Abdominal surgery patients	3751	KDIGO	6.9	Transient AKI: OR = 3.87, 95% CI 2.12–7.08, P < 0.001; Persistent AKI: OR = 23.70, 9.64–58.22, P < 0.001		Transient AKI: HR = 2.01, 95% CI 1.34–2.93, P = 0.001; Persistent AKI: HR = 6.20, 95% CI 3.00–11.43, P < 0.001	1
Bhatraju et al. [105]	Prospective	Hospitalized patients	1538	KDIGO	31	HR = 1.52, 95% CI 1.01–2.29, P = 0.04			5
Gameiro et al. [41]	Retrospective	Septic ICU		KDIGO	100	HR = 2.87, 95% CI 2.0–4.1, P < 0.001		HR = 1.51, 95% CI 1.0–2.2, P = 0.040	5
Cheng et al. [106]	Retrospective	Post-constrast hospitalized patients	34 709	European Society of Urogenital Radiology	0.83			Persistent renal dysfunction: OR = 3.685, 95% CI 1.628–8.340, P = 0.002	1
Coca et al. [31]	Prospective	Non-cardiac surgery diabetic patients	35 302	AKIN	17.8			AKIN 1: HR = 1.24, 95% CI 1.17–1.31; AKIN 2: HR = 1.64, 95% CI 1.43–1.88; AKIN 3: HR = 1.96, 95% CI 1.63–2.37	4

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The impact of recurrent episodes of AKI on prognosis is also reflected in a cohort of 3679 diabetic patients with preserved renal function analysed by Thakar et al. In this study, 30% of patients experienced >2 AKI episodes which had a cumulative risk effect for developing CKD [82].

Furthermore, in a cohort of 359 patients in which recurrent AKI was observed in 34% of cases, recurrent AKI was associated with increased development of CKD (HR = 2.2, 95% CI 1.09–4.3), increased risk of cardiovascular events and increased mortality risk (HR = 4.5, 95% CI 2.7–7.5) [83].

AKI recurrence has a strong impact on renal, cardiovascular and patient outcomes. So, to prevent recurrent AKI, it is important to identify at-risk patients. Older age [77, 79, 81], black race and Hispanic ethnicity, [77] diabetes, [77, 83] CVD, [77, 78, 83] decreased baseline kidney function, [77, 79, 81, 83] liver disease, [77, 78] cancer, [78] higher illness severity, [77, 81] proteinuria, [77] anaemia [77] and longer AKI duration [78] have been associated with incomplete renal recovery after AKI [79]. Impaired renal reserve and the lingering effects of acute illness or its therapies might contribute to AKI recurrence and outcomes in these patients. Strategies to reduce the incidence of recurrent AKI might improve the long-term outcomes.

CKD development and/or progression. Several studies have demonstrated the association of CKD development following AKI, which have been summarized in previous systematic reviews [71, 72]. It is, therefore, crucial to identify risk factors associated with CKD development (Table 3).

Coca et al. reported that AKI increased the risk of CKD by 8-fold (HR = 8.8, 95% CI 3.1–25.5) and the risk of end-stage kidney disease by 3-fold (HR = 3.1, 95% CI 1.9–5.0). Moreover, the risk was higher according to AKI severity (mild AKI HR = 2.3, 95% CI 1.7–3.3; severe AKI HR = 8.0, 95% CI 1.3–48.6) [72]. Similarly, See et al. demonstrated that the risk of CKD was 3-fold higher in AKI patients (HR = 2.67, 95% CI 1.99–3.58) [71].

The increased risk of development and/or progression of CKD as a long-term outcome associated with AKI have been demonstrated in multiple settings [47, 90]. Chawla et al. demonstrated an increased risk of adverse kidney events [long-term dialysis, 25% decrease in estimated glomerular filtration rate (eGFR) and death] in AKI patients in a cohort of 36 980 Veterans (HR = 2.07, 95% CI 1.99–2.16) [14]. A Swedish cohort of 97 782 patients critical care patients reported an increased rate of CKD [6.0% versus 0.44%, adjusted incidence rate ratio (IRR) 7.6] and end stage renal disease (ESRD) (3.9% versus 0.3%, adjusted IRR = 22.5) [93]. In 3245 cardiac surgery patients, the prevalence of CKD was significantly higher in AKI patients (6.8% versus 0.2%, P < 0.001; RR = 1.92, 95% CI 1.37–2.69) in the 2 years after surgery, even with complete recovery of renal function at discharge [94]. This was also reported in major abdominal surgery in a previous study of 390 patient in whom AKI was a risk factor for need for long-term dialysis and/or a 25% decrease in eGFR after hospital discharge (adjusted HR = 1.6, P = 0.046) [96].

The risk of CKD is also higher in relation to the severity of AKI as demonstrated in previous studies, and even higher in patients who require dialysis [84]. Ryden et al. studied 29 330 patients who underwent primary isolated coronary artery bypass grafting and demonstrated that the risk for ESRD increased with AKI severity, and was 2.92 (95% CI 1.87–4.55) for AKIN Stage 1 and 3.81 (95% CI 2.14–6.79) for AKIN Stages 2 and 3 [91]. In AKI requiring dialysis, the incidence rate of ESRD was 2.63/100 person-years in a study by Wald et al. (HR = 3.23, 95% CI 2.70–3.86) [84].

The risk of ESRD is higher in patients with previous CKD. Wu et al. reported an incidence rate of long-term dialysis of 17.8/100 person-years in patients with AKI-on-CKD when compared with patients without previous CKD [86].

Other than AKI severity, considering that even less severe stages of AKI are associated with long-term outcomes, the recovery of renal function after an AKI episode and its risk of developing CKD have also been studied.

Patients who recover renal function less often progress to CKD. Pannu et al. analysed long-term outcomes among 3231 survivors of hospitalization over a 6-year period, and reported an 2.1% incidence of ESRD and 9.8% of CKD in the AKI group, and demonstrated that patients who did not recover renal function after AKI had a higher risk of CKD and ESRD (HR = 4.13, 95% CI 3.38–5.04) [88]. On the contrary, in a retrospective cohort of 221 087 hospitalized patients by Heung et al. 31.8% of AKI patients progressed to CKD as compared to only 15.5% of non-AKI patients, on a 1-year follow-up (P < 0.001). In this study, even after recovery of AKI within 48 h, there was a relative risk of CKD progression which also increased associated with AKI severity [47]. Therefore, the duration of AKI might also impact on outcomes.

Indeed, a different threshold of AKI duration has been reported in the prospective study by Bhatraju et al. of 1538 participants in which non-recovery of renal function within the first 72 h after AKI was associated with a 51% greater risk of CKD development or dialysis requirement or death (95% CI 22–88%, P < 0.001) [105]. However, the risk of CKD development was still higher than non-AKI patients.

Accordingly, the presence of AKD has also been associated with CKD development. Among 225 patients undergoing PCI after myocardial infarction, 58.5% of AKD patients developed new or progressed CKD [100]. In 256 septic-AKI patients, AKD was also independently associated with adverse renal outcomes (HR = 2.87, 95% CI 2.0–4.1, P < 0.001) [107].

The majority of studies assessed the link between AKI and CKD based on eGFR decline, still more recent studies have identified new-onset albuminuria following AKI as a marker of CKD progression.

Proteinuria is a well-established and risk factor for CKD progression and cardiovascular events [108–110]. Interestingly, in a retrospective cohort of 657 840 patients, the risk of developing or worsening proteinuria was higher in AKI patients (OR = 1.39, 95% CI 1.33–1.46) and increased according to AKI severity [90]. Also, proteinuria and albuminuria have been more prevalent in AKI patients and associated with CKD progression [90]. Parr et al. also demonstrated that AKI patients had increased risk of developing proteinuria (OR range 1.20–1.39), which also increased according to AKI severity [111].

Factors associated with higher risk of CKD following AKI were previous increased baseline SCr, male gender, African American race, older age, diabetes, previous CVD, hypoalbuminaemia, lower haematocrit, AKI severity, duration and recovery pattern of AKI, recurrent AKI episodes (Figure 5) [14, 59, 80, 84, 87, 93, 96, 103, 112, 113].

Development of CKD after AKI is also a risk factor for the development of cardiovascular events and for long-term mortality. Cabrales et al. demonstrated that on a 4-year follow-up after an AKI episode, patients with hypertension (OR = 1.62, 95% CI 1.2–2.6) had a higher risk of developing CKD, patients with previous CKD had a higher risk of CKD progression. Furthermore, CKD patients had an increased risk of cardiovascular events (62.7 versus 21.7%, P < 0.05), and that mortality risk was increased by 4-fold (OR = 4.3, 95% CI 1.13–4.90) [101].

Furthermore, CKD after AKI has also been associated with increased mortality risk. For instance, in 634 AKI patients, Lai *et al.* found that the long-term mortality risk increased as kidney function declined during follow-up [114]. In 425 critically ill AKI patients, development of CKD was an independent predictor of mortality (OR = 4.3, 95% CI 2.9–6.2) [87].

Long-term cardiovascular outcomes

AKI is associated with increased long-term cardiovascular morbidity [115]. Odutayo *et al.* performed a systematic review and reported that AKI was associated with an 86% increased risk of cardiovascular mortality and a 38% increased risk of major cardiovascular events, namely development of chronic heart failure, acute myocardial infarction and stroke [116].

The relationship between CKD and CVD is well documented [115]. The term cardiorenal syndrome has been proposed to describe the complex bidirectional interactions between heart and kidneys [115, 117]. AKI may lead to direct and indirect effect on cardiac function and structure and thus increase the risk of cardiovascular events. The pathophysiological processes include activation of the sympathetic nervous system, activation of the RAAS, endothelial dysfunction, inflammation, cardiac fibrosis, volume expansion, hypertension, electrolyte disturbances, acidaemia and anaemia [115, 118].

AKI has been associated with development with blood pressure elevation. In a retrospective study of 43 611 hospitalized patients, AKI was associated with a 22% increased risk of hypertension within a 2-year follow-up, which greater according to AKI severity [119]. Indeed, in experimental studies, it has been reported that sodium-sensitive hypertension develops after an ischaemic renal event, due to impaired renal sodium excretion [120].

The association between AKI and CVD has been demonstrated in several studies (Table 3). In a retrospective study of US Veterans, Chawla *et al.* reported an increased risk of cardiovascular outcomes, namely myocardial infarction, stroke or heart failure (HR = 1.24, 95% CI 1.18–1.30), in AKI patients [14]. In a cohort of 4742 cardiac surgery patients the risk of myocardial infarction, heart failure and stroke was significantly increased in AKI patients on a 5-year follow-up (HR = 1.37, 95% CI 1.05–1.80). Additionally, AKI was associated with an increase in both short- and long-term mortality [95]. Wu *et al.* demonstrated an incidence rate of coronary events of 19.8/1000 person-years (HR = 1.67, 95% CI 1.36–2.04) independently of progression to CKD [92]. Similar results have also been reported in non-cardiovascular surgery patients [102]. Also, in a *post hoc* analysis of 9361 patients enrolled in the Systolic Blood Pressure Intervention Trial, AKI patients had a higher risk of cardiovascular events (HR = 1.52, 95% CI 1.05–2.20).

The risk of cardiovascular events increases according to AKI severity [98, 103]. Lee *et al.* reported that AKI patients who required dialysis more frequently developed cardiovascular events (HR = 1.97, 95% CI 1.75–2.23) and that this risk was high even patients who recovered renal function (HR = 1.73, 95% CI 1.54–1.95) [103]. Furthermore, even small transient and changes in renal function have been associated with increased risk of cardiovascular events [85].

Parikh conducted a study on 968 adults who underwent cardiac surgery which also demonstrated the association of AKI and AKI severity and an increased risk of cardiovascular events [98]. Interestingly, in this study, there was a significant association between peak postoperative cardiac injury biomarkers and CV outcomes while there was no association between peak postoperative urinary injury biomarkers and CV outcomes [98]. This further reinforces the systemic and haemodynamic effects of AKI on cardiac dysfunction.

Reported factors associated with higher risk of CVD following AKI were older age, CKD, diabetes and previous cardiovascular events (Figure 5) [14, 15, 98, 121].

Long-term mortality

The association between AKI and mortality in the long-term is well recognized (Table 3). Interestingly, this association is independent of pre-existing CKD. In a review by Coca *et al.*, the pooled mortality was 8.9 deaths/100 person-years following AKI [122]. Similarly, a more recent review by See *et al.* reported a pooled mortality of 13.2 deaths/100 person-year after AKI [71].

Chawla *et al.* demonstrated that the risk of mortality after AKI (HR = 1.85, 95% CI 1.76–1.94, P < 0.001) was almost 2-fold higher than the risk of mortality after myocardial infarction [14]. This was an important finding which raised awareness to the detrimental impact of AKI on long-term outcomes.

In a longitudinal cohort of 7075 adult patients who were submitted to cardiac surgery, AKI was a predictor of mortality in the 5 years following surgery (30 days to 1 year: HR = 1.834, 95% CI 1.459–2.306; 1–3 years: HR = 1.285, 95% CI 1.023–1.610; and 3–5 years: HR = 1.330, 95% CI 1.123–1.750) [99].

The increased severity of AKI is also associated with increased mortality risk [71, 122]. Fuchs *et al.* analysed the long-term outcomes of 12 399 survivors from an ICU admission and reported that patients with AKI Stage 3 AKIN had a 61% higher mortality risk on a 2-year follow-up compared with patients without AKI (P = 0.001) [89]. Less severe changes in renal function were also associated with mortality risk, though this risk was progressively higher with the increasing severity of AKI (AKIN 1: HR = 1.12, AKIN 2: 1.19, AKIN 3: 1.24, compared with no AKI, P < 0.05) [89]. Soliman *et al.* also demonstrated that moderate or severe AKI was associated with higher mortality in 2420 patients, 1 year after ICU admission [Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) injury adjusted relative risk 1.14, 95% CI 1.01–1.29; P = 0.03; RIFLE failure adjusted relative risk 1.25, 95% CI 1.01, 1.55; P = 0.04] [97]. Another cohort demonstrated that patients who required RRT had the highest risk of long-term mortality (adjusted HR = 2.65, 95% CI 2.0–3.52) [31].

The duration of AKI has also been studied as a predictor of long-term mortality. Coca *et al.* prospectively studied 35 302 diabetic patients who underwent non-cardiac surgery and described that not only the severity but also the duration of AKI decreased long-term survival. Remarkably, patients with longer duration of AKI had higher mortality in every stage of AKIN (log-rank test P < 0.001) [31]. Similarly, Cheng *et al.* demonstrated that compared with transient renal dysfunction, patients with persistent AKI following contrast administration had higher mortality after 1 year (RR = 3.768, 95% CI 1.612–8.810; RR = 4.106, 95% CI 1.765–9.551) [106]. Still, transient changes in renal function are also associated with higher mortality when compared with patients without AKI. Mizota *et al.* reported that transient AKI was frequent in patients undergoing major abdominal surgery and that compared to patients without AKI, patients with transient (adjusted HR = 2.01, 95% CI 1.34–2.93, P = 0.001) and persistent AKI (adjusted HR = 6.20, 95% CI 3.00–11.43, P < 0.001) had increased mortality rates on a 1-year follow-up [104].

Importantly, recovery of renal function after AKI appears to be predictor of better long-term survival. In a prospective cohort of 425 critically ill patients the mortality rate patients who

recovered renal function after AKI was lower than patients with CKD (46% versus 83%, P < 0.001) [87]. In a study of 1742 septic patients, it was reported that patients who recovered renal function after AKI had similar survival compared with patients without AKI (HR = 1.01, 95% CI 0.69–1.47, P = 0.96) over a median follow-up of 1.7 years [123]. Kofman et al. evaluated the incidence and prognosis of AKD after AKI and described that development of AKD was associated with increased long-term mortality in 225 patients with myocardial infarction (35% versus 17%, P < 0.001) [100].

As previously described, development of CKD and cardiovascular events after AKI is also associated with higher mortality rates.

Whether AKI directly contributes to mortality or serves as a surrogate marker of illness severity in higher-risk patients is still uncertain. The most frequently reported causes of mortality have been CVD, infections and cancer [87, 124].

Other than AKI severity, duration and renal recovery; lower baseline kidney function, male gender, older age, presence of comorbidities (diabetes, hypertension, CVD and cancer) and hypoalbuminaemia have also been associated with increased mortality risk following AKI (Figure 5) [14, 99, 123, 125–127].

Follow-up care after AKI

Despite consistent evidence that AKI has a negative impact on long-term outcomes, the reported rates of nephrology follow-up after AKI are low [128, 129]. Furthermore, to date, there is no standardized AKI or AKD follow-up care.

The US Renal Data System annual report of 2015 states that only 19% of patients had a nephrology follow-up at 12 months after an AKI hospitalization [130]. Siew et al. reported nephrology referral in only 4% of patients at 3 months and only 9% at 1 year, despite the fact that the mortality rate during this period was 22% [16]. Patients who were not referred to nephrology consult were slightly older, but had better kidney function and were less likely to have diabetes or heart failure [16]. An important limitation of this study is that the reasons for referral or non-referral are not reported, namely decisions to limit care.

The benefit of nephrology referral is uncertain, though, Harel et al. reported that on the 41% of 3877 AKI patients who were referred to nephrology follow-up within 90 days there was a 24% mortality reduction in 2 years of follow-up, in a retrospective analysis [131]. Interestingly, to reduce survival bias, patients were matched using a propensity score for comorbidities and required a minimum survival period following hospital discharge of 90 days, to exclude patients with high disease burden in whom nephrology follow-up would be of less benefit.

The exact factors that contribute to this survival benefit are not completely clarified; however, recognition and treatment of cardiovascular risk factors and CKD complications are most likely implicated. Additionally, the nephrologist can be useful in patients with decision to limit care, as part of the palliative care team.

During the AKI episode the main goal should be the recovery to baseline kidney function in the shortest period of time in order to reduce the duration and disease severity [132–134]. After discharge it is crucial to preserve renal function and prevent further deterioration, by controlling hypertension, proteinuria, diabetes mellitus and CVD [135].

The current recommendations by the KDIGO and the ADQI state that patients should be followed by a nephrologist at least 3 months after an AKI episode in order to estimate kidney

recovery and/or progression to CKD, or progressive CKD [18, 133]. The follow-up assessment should include kidney function and proteinuria, medication reconciliation, patient education to nephrotoxic avoidance and strategies to prevent CKD progression [133, 136].

Prescribing RAAS inhibitors after an AKI episode is promising as it might decrease the loss of kidney function, decrease CVD events and decrease mortality [64, 137, 138]. Chou et al. prospectively analysed 587 patients who recovered kidney function after cardiac-surgery associated AKI, and demonstrated that prescription of RAAS inhibitors after kidney function recovery was independently associated with lower risk of CKD development (26.6% versus 42.2%, HR = 0.46, P < 0.001) [64]. A retrospective cohort of 46 253 AKI survivours who were prescribed RAAS inhibitors within 6 months of the AKI episode, demonstrated a decreased mortality risk after 2 years (HR = 0.85, 95% CI 0.81–0.89). However, there was an increased risk of hospitalization for a renal cause [137]. Still, the risk of AKI recurrence associated with RAAS inhibitors has not been demonstrated in more recent studies [139].

Another promising therapeutic intervention is the use of statins. On a retrospective cohort of 19 707 patients with CKD after AKI, patients who were prescribed statins after AKI had lower rate of hospitalizations and mortality risk over a 2-year follow-up [75]. Still, timing of statin prescription was not assessed neither were some important covariates, namely blood pressure.

The use of RAAS inhibitors and statins is promising to reduce the cardiovascular risk after AKI, which has a significant prevalence in these patients. However, interventional and further observational studies are needed to establish the concrete benefit of RAAS inhibitors and/or statins after AKI and to define the adequate timing and dose to start these medications after AKI.

Several medications which can decrease renal function or are associated with adverse events due to drug accumulation in CKD patients must also be adjusted in high-risk patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) affect renal function due to prostaglandin inhibition and are associated with an increased risk of AKI and CKD [140]. AKI is predominantly haemodynamically mediated but can also be immune-mediated, and is higher in elderly patients and with concomitant use of RAAS inhibitors or diuretics [140]. The development of CKD appears to be associated with higher doses of NSAIDs [141]. Although the risk of adverse effects of NSAIDs following AKI has not been specifically evaluated it is important to recognize the increased risk of this population and to carefully prescribe these medications [141].

Given that the risk of hypoglycaemia after discharge following AKI has been reportedly higher in patients medicated with insulin and sulfonylurea, it is necessary to intervene and lower the risk of these episodes in patients medicated with glucose-lowering agents with renal excretion [142]. The use of sodium–glucose cotransporter 2 (SGLT2) inhibitors to improve glycaemic control after AKI is promising as these have been associated with decreasing the risk of cardiovascular events and CKD progression [143]. Still, further randomized trials are necessary to assess the safety of these drugs in patients with recent AKI or CKD patients.

Assessing which patients are at higher risk for CKD development, cardiovascular events and long-term mortality after AKI are therefore crucial (Figure 5). Prediction models applied at discharge could estimate the risk of adverse outcomes and target patients at risk with specialized interventions [144]. The use of biomarkers to estimate risk is also promising as higher levels of

Table 4. List of research needs on the period after AKI

Research requirements
Optimal timing for nephrology follow-up
Biomarkers of the transition from AKI to CKD
Benefits of RAAS inhibitors, statins, SGLT2 inhibitors
Benefits of other anti-fibrotic or anti-inflammatory drugs

NGAL, IL-18, KIM-1, albuminuria, TIMP-2 × IGFBP7 have been associated with increased long-term adverse outcomes after AKI [69, 145]. To date, only NGAL and TIMP-2 × IGFBP7 have been approved, though their widespread use in clinical practice is still distant. These biomarkers might provide prognostic information during the AKI period, although no studies have analysed patient follow-up assessed with these biomarkers.

Currently, two randomized clinical trials are comparing standardized care to nephrology follow-up [146, 147]. The FUSION trial will compare patients with a referral to family physician after hospitalization and later local nephrology follow-up if considered appropriate by the physician versus patients who will be referred to an AKI follow-up clinic within 30 days after discharged and routine laboratory every 3 months, and assess patient outcomes on a 5-year follow-up [146]. This trial The AFTER-AKI trial will compare patients discharged with usual discharge protocols and patients who will receive specific follow-up protocols based on their risk of CKD, and assess outcomes after 1-year follow-up [147]. These are highly anticipated to clarify the importance of specialized care after AKI on improving patient outcomes.

Further research is essential to stratify high-risk patients, define timing for nephrology follow-up and to develop strategies to improve patient outcomes.

CONCLUSION

It is crucial to stop regarding AKI as a short-term reversible condition and to raise awareness on the long-term complications, such as progression to CKD, increased cardiovascular events and mortality. Whether AKI is a marker of patients with more co-morbidities and increased risk for poor prognosis or directly contributes to adverse outcomes is still unclear.

It is evident that AKI survivors should have specialized long-term follow-up. Nephrology follow-up is crucial to assess kidney function after AKI, perform medication reconciliation, educate patients on nephrotoxic avoidance and implement strategies to prevent CKD progression.

Still, further investigation is required on assessment of biomarkers of renal recovery and worse renal and vital prognosis, and on assessment of safety and dosing of specific therapeutic strategies (RAAS inhibitors, statins and SGLT2 inhibitors) to prevent CKD and CVD after AKI, and in defining optimal follow-up timing (Table 4).

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AUTHORS' CONTRIBUTIONS

J.G. made substantial contributions to the study concept and was involved in drafting the manuscript, F.M. made substantial contributions to the study design and J.A.L. was involved in revising it critically for intellectual content.

CONFLICT OF INTEREST STATEMENT

The authors declare there is no conflict of interest.

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