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REVIEW

Renal recovery after acute kidney injury

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Abstract

Acute kidney injury (AKI) is a frequent complication of critical illness and carries a significant risk of short- and long-term mortality, chronic kidney disease (CKD) and cardiovascular events. The degree of renal recovery from AKI may substantially affect these long-term endpoints. Therefore maximising recovery of renal function should be the goal of any AKI prevention and treatment strategy. Defining renal recovery is far from straightforward due in part to the limitations of the tests available to assess renal function. Here, we discuss common pitfalls in the evaluation of renal recovery and provide suggestions for improved assessment in the future. We review the epidemiology of renal recovery and of the association between AKI and the development of CKD. Finally, we stress the importance of post-discharge follow-up of AKI patients and make suggestions for its incorporation into clinical practice. Summary key points are that risk factors for non-recovery of AKI are age, CKD, comorbidity, higher severity of AKI and acute disease scores. Second, AKI and CKD are mutually related and seem to have a common denominator. Third, despite its limitations full recovery of AKI may best be defined as the absence of AKI criteria, and partial recovery as a fall in AKI stage. Fourth, after an episode of AKI, serial follow-up measurements of serum creatinine and proteinuria are warranted to diagnose renal impairment and prevent further progression. Measures to promote recovery are similar to those preventing renal harm. Specific interventions promoting repair are still experimental.

Keywords: Acute kidney injury, Acute kidney disease, Chronic kidney disease, Renal replacement therapy, Follow-up, Biomarkers

Introduction: why focus on recovery?

While acute renal impairment is sometimes thought of as a relatively trivial insult defined purely by changes in serum creatinine, the introduction and subsequent acceptance of the concept of acute kidney injury (AKI) has gradually alerted critical care and nephrology clinicians to potential late complications in AKI survivors. It is well recognised that progressive or persistent impairment in renal function may occur following an episode of AKI, with the potential to progress to end-stage kidney disease (ESKD) with dialysis dependence. However, the outcome from an episode of AKI cannot simply be regarded as the binary administration for chronic renal replacement therapy (RRT) or recovery. Several authors have highlighted the substantial risk of development and progression of chronic kidney disease (CKD), short of ESKD [1–11] which is in turn strongly associated with increased short- and long-term mortality [10, 12]. This association does not necessarily implicate causation but could also indicate a common underlying disease process (Fig. 1). The question thus arises 'What do we mean by renal recovery after AKI?' Furthermore, in the absence of an effective therapy to alter the acute course of established AKI, our current focus should be turned towards both AKI prevention and promotion of kidney repair in the recovery phase.

Pathophysiology of recovery

The mechanisms underlying the renal repair process after AKI have predominantly been studied in animal models

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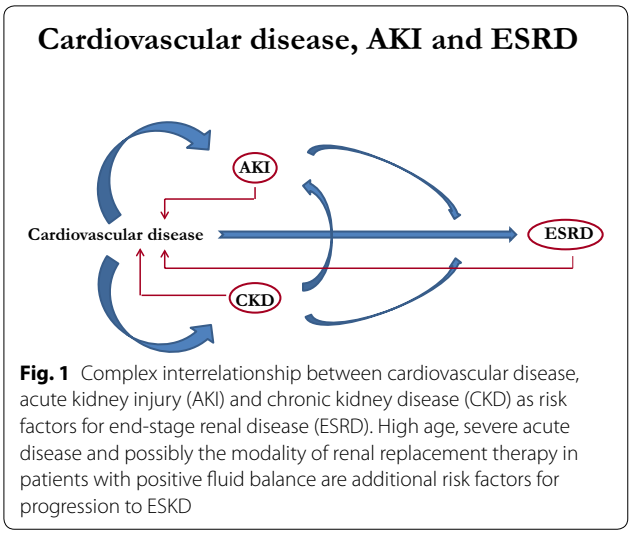

Fig. 1 Complex interrelationship between cardiovascular disease, acute kidney injury (AKI) and chronic kidney disease (CKD) as risk factors for end-stage renal disease (ESRD). High age, severe acute disease and possibly the modality of renal replacement therapy in patients with positive fluid balance are additional risk factors for progression to ESKD

of ischaemic AKI, characterized by loss of the brush border, principally in the proximal tubular epithelium, with inflammatory cell infiltration and epithelial cell sloughing, followed by repopulation of the damaged tubules by regenerating cells. After much debate as to whether the cells involved in this regenerative process are endogenous tubular epithelial cells, adult renal stem cells or bone marrow-derived stem cells, there is now increasing evidence that the repopulation mainly relies on surviving endogenous tubular cells with bone marrow-derived stem cells having at most a paracrine role through growth factor secretion [2].

Under certain circumstances, renal repair is maladaptive with inflammation, fibrosis and vascular rarefaction leading to persistent cell and tissue malfunction and eventually CKD. The frequency, severity, type and duration of injury as well the premorbid renal reserve (age, pre-existing CKD) seem to be risk factors for maladaptive repair. Both injured tubular epithelial cells and macrophages play an important role in this maladaptive repair process. Perturbations of the cell cycle with arrest in the G_2 phase and tubular cells failing to differentiate lead to production of proinflammatory and profibrotic signals and proliferation of the resident fibroblast population [2]. Whole organ gene expression profiling has been employed to identify molecular markers and regulatory pathways controlling the repair process [13] (Fig. 2). Understanding the mechanisms underlying maladaptive repair could potentially provide new targets for therapeutic intervention. In particular, strategies directed at inhibiting fibrosis or enhancing the endogenous repair processes may be promising.

Clinical definition of renal recovery

Pitfalls in evaluation of recovery

Assessment of baseline function

An adequate definition of renal recovery requires a reliable assessment of baseline kidney function to distinguish

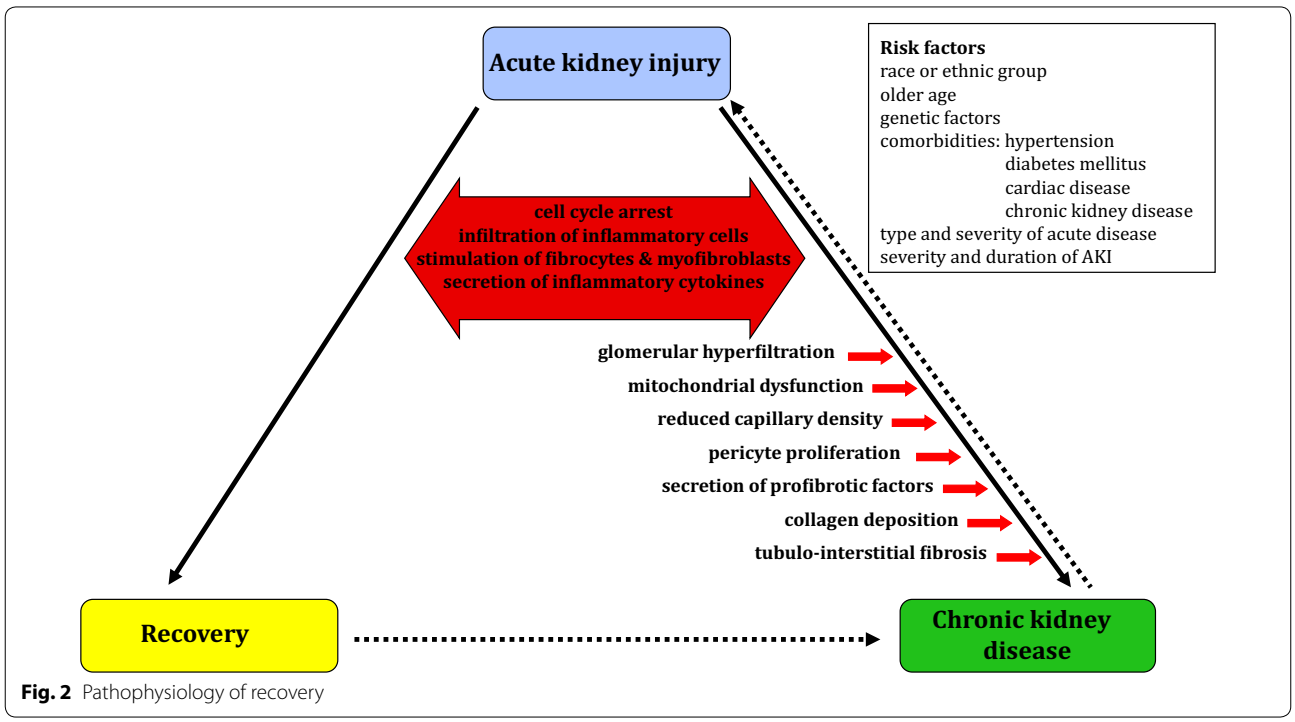

Fig. 2 Pathophysiology of recovery

non-recovery from pre-existing CKD. Efforts to obtain baseline kidney function, e.g. from the primary care or referring specialists, are therefore of utmost importance. The mean outpatient serum creatinine (SCr) (and the derived estimated glomerular filtration rate, eGFR) or, failing this, the most recent SCr measured between 7 and 365 days prior to the start of the acute illness is generally considered the best reflection of baseline kidney function [14]. Extremes in muscle mass or dietary protein intake may affect SCr independent of kidney function. Although use of cystatin C and cystatin-based eGFR equations may reduce this problem [15], a baseline cystatin C level is rarely available. Another potential shortcoming of SCr, and the derived eGFR, is insensitivity to detect mild underlying CKD and the inability to detect the pre-existing presence or absence of renal functional reserve [16].

In the absence of a known baseline SCr the Kidney Diseases Improving Global outcomes (KDIGO) AKI workgroup suggests estimation of baseline through use of the Modification of Diet in Renal Disease (MDRD) equation [17]. This estimation assumes that patients have a baseline eGFR of 75 mL/min/1.73 m^2, does not allow one to detect the presence of pre-existing CKD or well-preserved renal function and will undoubtedly confound the evaluation of recovery [18]. In addition, the absence of a baseline SCr is usually non-random as demonstrated in a recent analysis which found less complete recovery in patients with unknown or missing baseline SCr compared with those with a known baseline [19]. An alternative is to use admission creatinine as a baseline. However, this ignores pre-admission AKI and has many other potential confounders including the absence of steady state, the effect of dilution after fluid resuscitation and reduced creatinine production in critical illness [20].

Defining the population

While most studies on renal recovery exclude prior ESKD (as defined by need for chronic dialysis), the handling of pre-existing CKD is variable. Furthermore, recovery has been reported in different populations (hospitalized versus ICU patients, general ICU versus specific surgical or medical populations, inclusion or exclusion of less severe forms of AKI). Whether recovery should be evaluated in all AKI patients or in survivors only depends on the setting. In a clinical trial evaluating an intervention to improve recovery, mortality should be treated as a competing endpoint. However, recovery in survivors may also be relevant to assess at the bedside [19].

Timing of recovery assessment

In the current literature, the timing for the evaluation of renal recovery varies considerably. Some studies determine "recovery" after 3–7 days to make the distinction between transient and persistent AKI. Recent evidence suggests that the time pattern of changes in kidney function and relapses after initial "reversal" may also be associated with mortality [12, 21]. Most studies report recovery at hospital discharge. However, its evaluation at a fixed time point, e.g. at 3 months, allowing one to mark the transition from AKI to CKD, would be more appropriate. Delaying the assessment might also reduce the problem of the impact of sarcopenia on SCr levels. The recent Acute Disease Quality Initiative (ADQI) conference suggests differentiating AKI (first 7 days) from acute kidney disease (AKD) (AKI persisting for 7–90 days) and CKD (after 90 days), which may provide a framework for defining recovery in terms of time after the sentinel event (Fig. 3). While AKD was initially proposed to encompass any acute condition that impacts on longer-term kidney function [22], this more recent ADQI proposal further refines the criteria with the addition of a staging system [23].

Defining recovery

In the past, renal recovery was often defined as independence from RRT following dialysis-requiring AKI. More recently, non-recovery from less severe AKI has received more attention due to its association with adverse long-term outcomes [1, 21]. Despite many limitations the most obvious definition of full recovery from AKI is the absence of AKI criteria. Partial recovery can then be defined as a fall in AKI stage. Recovery may occur early after the insult leading to AKI or later during the phase of AKD (Fig. 3). However, it is important to appreciate that the use of the creatinine criteria may result in important underestimation of recovery in patients with unknown premorbid creatinine [18] or overestimation of recovery by ignoring the loss of muscle mass that occurs during critical illness [19, 24]. Tubular secretion of creatinine, the contribution of which increases with decreasing GFR, also results in overestimation of GFR by creatinine clearance. An alternative definition of non-recovery might be the presence of eGFR criteria for new or worsening CKD [25], which, however, still relies on SCr with its associated shortcomings.

Future directions

An ideal definition of recovery would compare the gold standard of GFR measurement before and after the episode of AKI. Even better would be the inclusion of an assessment of renal functional reserve before and after the episode of AKI. However, outside predictable events such as elective major surgery, accrual of such data is highly unlikely. Despite this, there are potential avenues for improved assessment of renal recovery which are discussed below.

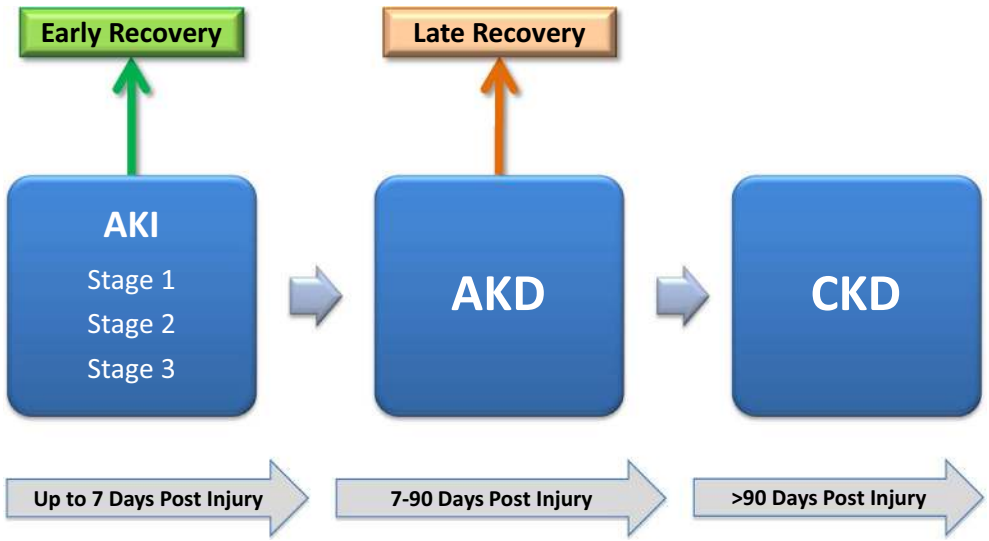

Fig. 3 AKI, AKD, CKD and time course of recovery. Recovery may occur early during acute kidney injury (AKI) up to 7 days after the insult, or later during acute kidney disease (AKD), between 7 days and 3 months after the insult to the kidney

Measurement of creatinine clearance

A potential avenue for exploration is the determination of the measured creatinine clearance at ICU discharge from a timed urinary collection coupled with a serum creatinine determination. Such an estimate of GFR is not without its detractors but is readily available and economical. Since premorbid creatinine clearance will usually not be available, defining recovery by this parameter assumes that the estimation of premorbid GFR with predictive equations is reliable and does not account for overestimation of glomerular filtration by creatinine clearance due to tubular creatinine excretion [19]. However, measuring creatinine clearance at ICU or hospital discharge may serve as a baseline for the follow-up.

Measurement of renal functional reserve

Renal functional reserve is defined as the increase in GFR after a stress test (e.g. an acute protein load [26]). Its measurement is difficult to perform in the ICU and few, if any, patients have such data available prior to an AKI event. However, assessing renal reserve could be useful to identify patients who are at increased risk of further progressive CKD or recurrent AKI (Table 1).

Kinetic eGFR

Kinetic eGFR is a mathematical method to estimate underlying renal function from the rate of change of creatinine during non-steady state conditions and has been proposed for the earlier detection of changes in GFR, both during development and recovery of AKI [27, 28]. However, in the critically ill there are several potential confounders that affect measured SCr concentrations and the eGFR, including assumptions regarding maximal rise in creatinine, reductions in creatinine production and changes in the volume of distribution. Although in comparison with novel AKI biomarkers, this technique has been shown to perform as well or better in predicting short-term recovery of kidney function (within 48 h) [28], the assumption that muscle mass is constant makes it less useful in assessing kidney function including recovery over a longer time-period in ICU patients. Measurement and correction of kinetic eGFR for muscle mass loss may be a way of improving this method.

Table 1 Risk factors for short-term non-recovery of renal function

Patient-related risk factors	Age Race ethnicity Genetic factors Chronic kidney disease Comorbidity
Severity of acute disease	High illness severity Haemodynamic instability Medical admission
Severity of AKI	Higher KDIGO stage

AKI acute kidney injury, *KDIGO* kidney disease improving global outcomes

Real-time GFR monitoring

Real-time GFR monitoring techniques are still experimental [29, 30], but nearing clinical implementation. The development of such systems will clearly aid in identifying individuals who have not recovered full function [31].

Biomarkers for (non)recovery

The limitations of both SCr and urine output as early indicators of AKI are well documented and have led to the pursuit of robust early markers of kidney damage. These biomarkers can be broadly classified as inflammatory biomarkers [e.g. neutrophil gelatinase-associated lipocalin (NGAL), interleukin (IL)-6 and IL-18], cell injury biomarkers [e.g. kidney injury molecule-1 (KIM-1) and liver fatty acid binding protein (L-FABP)] and markers of cell cycle arrest [e.g. insulin growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase 2 (TIMP-2)] (Table 2).

Few studies have evaluated these classical injury markers for their ability to predict recovery. Currently, NGAL has received most attention in this context. Plasma NGAL, measured on the first day of AKI stage 3, has been shown to be a reasonable predictor of failure to recover in a cohort of patients with community-acquired pneumonia, many of whom were not in the ICU [32]. A small substudy of the VA/NIH Acute Renal Failure Trial Network Study found that, in addition to age and a high Charlson comorbidity index, higher concentrations of a panel of urinary biomarkers at day 14 after commencement of RRT may improve the prediction of non-recovery/dialysis dependence at 60 days [33]. However, the investigators used a combined endpoint of death or renal non-recovery and only had 25 deaths and 13 non-recovery patients. Similarly, a panel of biomarkers applied to patients with AKI requiring RRT demonstrated that decreasing urinary NGAL during the first 14 days following AKI was associated with a reduced need for renal support at 60 days [34]. This study clearly highlights the value of repeated measures over single values. KIM-1 and L-FABP have also been proposed as a marker of renal recovery after AKI [35, 36]. Similarly the product of the more recently described G_1 cell cycle arrest markers of renal stress TIMP-2 and IGFBP7 ([TIMP-2] × [IGFBP7]) predicted short-term renal recovery/non-recovery within 48 h in 57 patients with early AKI [37].

Table 2 Biomarkers of short-term acute kidney injury (AKI) recovery versus persistence to acute kidney disease (AKD)

AKI biomarker	Characteristics	Clinical setting	Outcome
Angiotensinogen	453 amino acid protein; precursor of angiotensin I	Acute CRS Cardiac surgery ICU	AKI progression
Cystatin C	13 kDa cysteine protease inhibitor produced by all nucleated human cells; undergoes glomerular filtration	ICU	RRT
Hepatocyte growth factor	Antifibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI	ICU	RRT
IGFBP7 TIMP-2	29 kDa and 21 kDa proteins involved in cell cycle arrest; released into urine after tubular cell stress	ICU Cardiac surgery	RRT
IL-18	18 kDa pro-inflammatory cytokine; regulates innate and adaptive immunity; released into urine after proximal tubular cell injury	ICU Acute CRS Cardiac surgery Renal transplantation	AKI progression RRT DGF
KIM-1	39 kDa transmembrane glycoprotein involved in tubular regeneration; released into urine following ischaemic or nephrotoxic tubular cell damage	ICU Hospitalised patients Renal transplantation	AKI progression Need for RRT DGF
L-FABP	14 kDa intracellular lipid chaperone produced in proximal tubular cells; aids in regulation of fatty acid uptake and intracellular transport; excretion into urine after tubular injury	ICU Cardiac surgery	AKI progression RRT
MicroRNA	Endogenous single-stranded molecules of non-coding nucleotides; upregulated following tubular cell injury and cell proliferation; detectable in plasma and urine	ICU Cardiac surgery	AKI progression RRT
NAG	>130 kDa lysosomal enzyme; produced in proximal and distal tubular cells; released into urine after tubular cell injury	Hospitalised patients	RRT
NGAL	At least three different types: Monomeric 25 kDa glycoprotein produced by neutrophils and epithelial cells, including renal tubules Homodimeric 45 kDa protein produced by neutrophils Heterodimeric 135 kDa protein produced by renal tubular cells released into urine following systemic production or tubular injury	ICU Cardiac surgery Acute CRS Renal transplantation	AKI progression RRT DGF

Relevant references are mentioned in the text

AKI acute kidney injury, *CRS* cardiorenal syndrome, *DGF* delayed graft function, *ICU* intensive care unit, *IGFBP-7* insulin-like growth factor binding protein 7, *IL-18* interleukin 18, *L-FABP* liver-type fatty acid-binding protein, *KIM-1* kidney injury molecule-1, *NAG N*-acetyl-β-D-glucosaminidase, *NGAL* neutrophil gelatinase-associated lipocalin, *TIMP-2* tissue metalloproteinase 2, *RRT* renal replacement therapy, *kDa* kilodalton

Even less data is available on biomarkers that are specific for the repair process. In the setting of CKD, transforming growth factor beta (TGFβ), monocyte chemoattractant protein-1 (MCP-1) and matrix metalloproteinase protein-2 (MMP-2) have been shown to correlate with fibrosis and CKD progression [38]. After renal transplantation, urinary YKL-40, a repair phase protein, in the donor is independently associated with recovery from AKI and delayed graft function [39]. Dipstick albuminuria greater than 30 mg/dL is independently associated with lower rates of AKI recovery at 30 days in patients with sepsis [40]. Another promising biomarker for recovery is osteopontin [41, 42].

In general, trials evaluating biomarkers for prediction of recovery after AKI have been small and focussed predominantly on the differentiation between transient AKI and AKD.

Identification and Validation of Biomarkers of Acute Kidney Injury Recovery (ClinicalTrials.gov Identifier: NCT01868724) was a multicentre study to validate biomarkers specifically for major adverse kidney event (MAKE) and major adverse cardiac events (MACE) following an episode of AKI in ICU. The results are still awaited. Hopefully, the increasing insights into the molecular mechanisms of renal recovery will lead to new biomarkers specific to the repair process.

Potential markers of tubular function

One area that has received little attention in the post AKI period is that of tubular function. In CKD, proteinuria is the best predictor of both disease progression and ESKD over and above hypertension [43] which may arise because of both increased glomerular permeability and reduced tubular uptake of filtered protein. A few studies have highlighted that patients with preoperative proteinuria are at increased risk of AKI particularly after cardiac surgery [44, 45] and after severe burns [46]. Moreover, (tubular) proteinuria has been found to be associated with worse outcomes in the critically ill including the rate of AKI and long-term kidney function [47–49]. Other markers of tubular function have not been studied in any detail. Since proteinuria is known to be a modifiable risk factor in CKD, such assessment should be mandated in the follow-up of patients with AKI.

Epidemiology of renal outcome after AKI

Short-term renal outcome

Rates of non-recovery from dialysis-requiring AKI differ dramatically among populations and can vary between 0% and 40% [12, 50]. Differences in the indications and thresholds for starting RRT may account for some variability. Other studies have evaluated recovery from all AKI (including less severe forms) and reported complete recovery rates between 33% and 90% [12, 19, 32, 51–57]. However, the use of different definitions of AKI (with or without inclusion of the urine output criteria, with inclusion or exclusion of less severe forms), different definitions of recovery, the variable case-mix (surgical, medical or mixed population, inclusion or exclusion of patients with CKD, evaluation in survivors only) and differences in timing of assessment of recovery prevent a direct comparison of the results. Last, inclusion of patients dying during ICU stay strongly affects recovery rate, recovery being a time-dependent process and death during ICU stay acting as a potent confounder [19].

Long-term renal outcome

The association between AKI and subsequent progression to CKD has been highlighted by recent epidemiological studies [1, 3, 5, 6, 10, 21, 34, 58–62], although a causal relation cannot be proven. The association between AKI and CKD is complex and multidirectional so that CKD evolution may be either through non-recovery from AKI, de-novo development of CKD after recovery from AKI or progression of pre-existing CKD. In patients without prior CKD who have complete recovery of renal function, the risk of progressive CKD may be low [63]. However other authors have demonstrated a substantial incidence of de novo CKD and death in survivors of AKI, including those who do not require RRT [60].

As outlined, most studies demonstrate that the risk for ESKD after AKI is increased (Table 3) [10, 62]. Most studies on long-term kidney outcome are limited to patients receiving RRT and suggest that dialysis dependency at 90 days may approach up to 30% [10, 11, 50, 64, 65]. A large Danish registry study comprising 3062 ICU patients treated with RRT (among a total of 107,937 ICU patients) suggested a 5-year cumulative risk of ESKD of 11.7% (95% CI 10.5–13.0) [6]—in keeping with a Swedish registry study comprising 998 RRT-treated AKI patients [66]. The Danish registry study [6] revealed an adjusted HR of 105 (95% CI 78–142) for ESKD at 180 days for RRT-treated AKI patients compared to other critically ill patients (Table 3). The absolute risk difference was highest among those RRT-AKI patients with pre-existing CKD, and the relative risk of ESKD was highest among younger RRT-AKI patients, those with previous CKD, and those with elective surgery. Death and chronic dialysis treatment are competing risks which should be included in the analysis [67]. The follow-up study by the RENAL investigators [65] showed that the risk of dying was much greater than the risk of ESKD.

Risk factors/predictors for non-recovery

Risk factors for non-recovery after AKI include age, comorbidity, severity of acute disease and potentially the

Table 3 Long-term risk of end-stage kidney disease (ESKD) after acute kidney injury (AKI) and renal replacement therapy (RRT) treated AKI

AKI stage	Absolute risk (%)/at time	Hazard ratio, HR (95% CI) over time
AKI (all stages) vs. non-AKI	2% vs. 0.08%/1 year [62] 3.9% vs. 0.3%/5 year	HR 3.1 (1.9–5.0) per 100 patient-years [10]
RRT-treated AKI	90 days: 30% [10, 11, 50], 25% [64], 5.4% [65] 180 days: 8.5% [6] 1 year: 20% [64] 5 years: 11.7% (cumulative risk) [6] 7 years: 3.4% (new ESKD) [66]	Up to 180 days: HR 105 (78–148) vs. critically ill [6] From 80 days to 5 years: HR 6.2(4.7–8.1) vs. critically ill [6]

HR hazard ratio, *CI* confidence interval

modality of RRT [64, 68]. Among patient-related risk factors for non-recovery, high age [4, 12, 33, 61], the presence of CKD [8, 12, 34, 61, 69] and comorbidities such as hypertension, diabetes mellitus and cardiac disease [12, 33, 50] are the most frequently reported hazards. The common denominator is diminished glomerular reserve associated with age or chronic disease, suggesting a common underlying disease causing AKI and CKD. Type and severity of the acute disease process may also determine non-recovery. A high acuity of illness as reflected by higher APACHE or SAPS scores [12, 70, 71], a higher degree of haemodynamic instability [12, 34, 72], medical admission [12] or more severe AKI [12, 59, 73, 74] are additional risk factors for non-recovery. Interestingly, the evidence associating sepsis diagnosis with renal recovery after AKI is conflicting [12, 58]. In summary, putative mechanisms predisposing to renal non-recovery are exposure of a relatively decreased nephron mass to greater injury coupled with impaired or maladaptive repair mechanisms associated with age or chronic disease.

In general, patients needing RRT have a higher mortality and risk of non-recovery [64, 71, 75, 76]. Whereas some data suggest that RRT may be independently associated with impaired recovery following AKI [75], this issue remains controversial because of numerous unmeasured confounding variables. The impact of RRT modality on recovery remains controversial, too. While retrospective cohort studies suggest that initial use of CRRT is associated with less CKD than intermittent haemodialysis [64, 66], not all studies support this notion [77]. A meta-analysis showed that the benefit of CRRT was based on results in observational studies but not randomised controlled trials (RCTs) [68]. Interestingly, a recent retrospective observational French study used marginal structural modelling and found no differences in 30-day mortality and dialysis dependence (combined primary outcome) between continuous and intermittent RRT in the overall population. However, continuous treatment was associated with better 30-day survival without dialysis in patients with fluid overload, while it was associated with worse outcome in patients without haemodynamic instability at commencement of RRT [78]. Another recent multicentre retrospective cohort evaluating 638 patients alive at hospital discharge could not demonstrate any difference in renal recovery after adjustment for covariates between patients treated with intermittent haemodialysis or continuous RRT [77]. The authors suggest that when initial RRT modality is chosen primarily on haemodynamics, renal recovery in survivors is comparable between both modalities. Altogether, risk factors for non-recovery of AKI are higher age, CKD, comorbidity, higher severity of AKI and acute disease scores, while intermittent haemodialysis seems to be associated with non-recovery in patients with fluid overload at commencement of RRT.

Potential measures to promote renal recovery

General measures aimed at preventing AKI and protecting the kidney function should increase the chances for recovery [22, 23, 79]. This includes avoiding hyperglycaemia and nephrotoxins as well as using strict therapeutic drug monitoring if applicable. Episodes of renal hypoperfusion should be avoided by ensuring haemodynamic stability and adapting RRT modality to the haemodynamic situation and the presence of fluid overload [77, 78]. Specific interventions to promote recovery are still experimental. Promotion of cell proliferation and renal repair by clusterin [80, 81] and/or reducing post-injury fibrosis by AT1 receptor antagonism [82], pyridoxamine [83], alpha klotho [84], endothelial sphingosine-1-phosphate receptor 1 [85] or PTBA analogues [83] are some approaches that have shown promising results in animal studies.

Follow-up of AKI patients

Which patients require follow-up?

Follow-up for development of CKD should be considered in all patients who developed AKI, irrespective of the apparent degree of renal recovery. Importantly, while only a small proportion of AKI survivors may develop ESKD over time, many instead die, especially from cardiovascular causes [86]. CKD is indeed strongly associated with cardiovascular morbidity and mortality [87, 88]. In

younger survivors, development of hypertension and cardiovascular disease may accelerate CKD progression, so that ESKD may develop after many years even if there is an apparently good initial recovery. Thus, in all groups of AKI survivors there is great potential for interventions to improve longer-term outcomes.

How to organize follow-up?

In practice the main hurdle is identifying patients for follow-up. This can be problematic as hospital discharge may be many weeks or months following the episode of AKI with the discharging team often not involved in the active management of the patient during their critical illness. Currently only a minority of patients who require RRT in the ICU and recover renal function receive nephrology follow-up [89, 90], illustrating the need to establish robust mechanisms to ensure targeted AKI follow-up. Such services have been developed and piloted [91, 92], but generally remain dependent on referral of patients following inpatient nephrology consultation, emphasising the need for appropriate involvement of renal services as inpatients to allow appropriately targeted follow-up. Care pathways for follow-up should vary according to need. Patients with significant overt renal impairment at hospital discharge (e.g. eGFR less than 30 mL/min/m^2) require reassessment of renal function, probably within 2 weeks of discharge. In others, reassessment of renal function at 90 days after insult is more appropriate, to allow time for both recovery of muscle mass and any further recovery of renal function, permitting a clearer assessment of the new baseline renal function (Fig. 4). Timing and location of follow-up will be

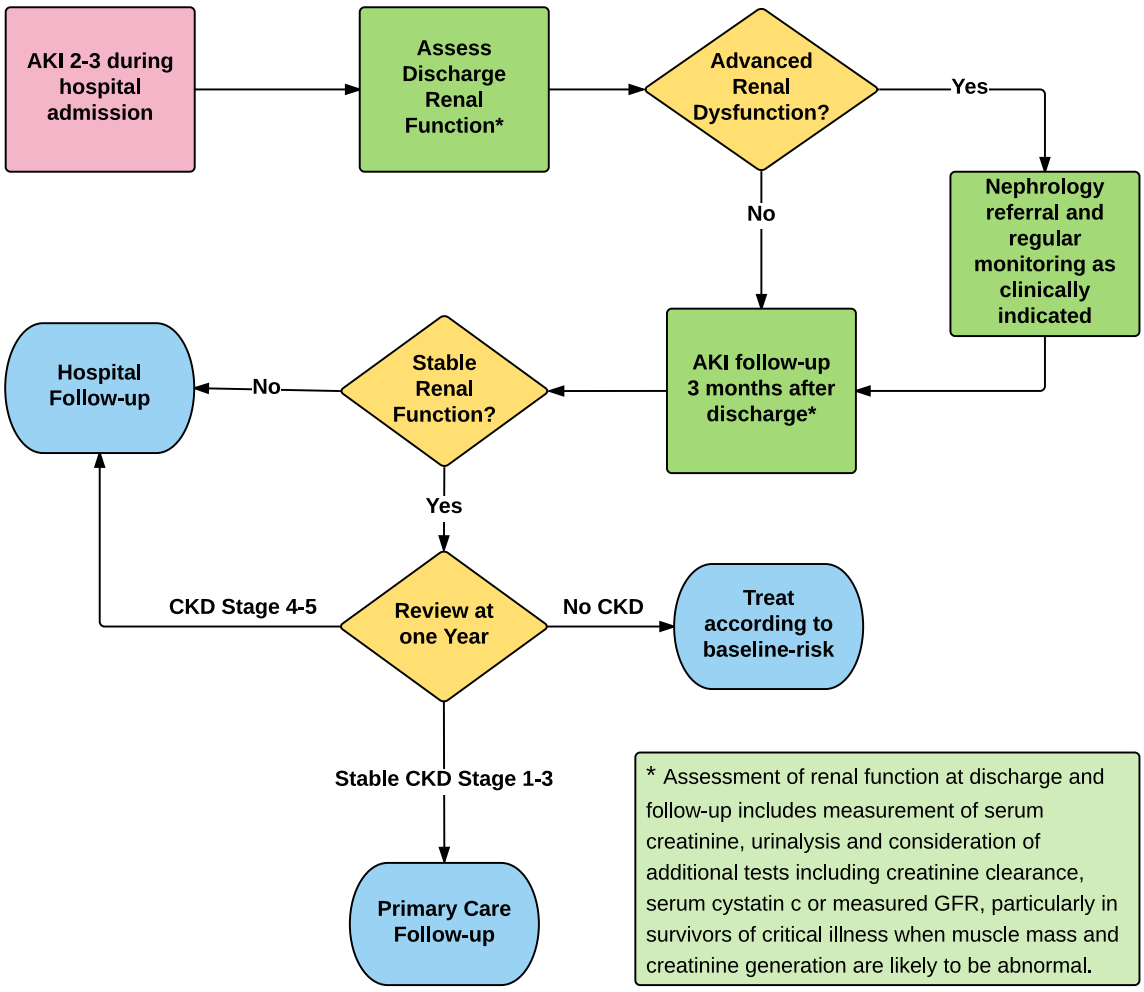

Fig. 4 Potential scheme for follow-up of acute kidney injury (AKI) stages 2–3 complicating critical illness. Potential scheme for follow-up of acute kidney injury (AKI) stages 2–3 complicating critical illness. Serial assessments at 3 months and 1 year after AKI are required to establish the presence and severity of chronic kidney disease (CKD) and establish prognosis. In most cases, long-term follow-up and treatment can be achieved outside of specialist nephrology services following CKD management guidelines

dependent on local resources; however, it is likely to be impracticable for all stage 1 AKI to receive follow-up in secondary care. Effective long-term management of CKD can be achieved in primary care, but this is only possible if patients are identified at discharge and appropriate clinical guidelines are provided by specialists.

Survivors of severe AKI requiring RRT and those with more advanced CKD may specifically benefit from specialist nephrology review [93]. Even at 3 months, creatinine may not accurately reflect GFR in many survivors of critical illness. Measurement of serum cystatin C, urinary creatinine clearance or even, theoretically, formal measurement of GFR may be required in patients with significant loss of muscle mass. Besides measurement of GFR, CKD assessment requires an assessment of proteinuria (urinary protein-to-creatinine ratio). Proteinuria, a common outcome after AKI even in the absence of overt renal dysfunction [94], potentially indicates underlying hyperfiltration and loss of renal reserve; however, irrespective of the underlying mechanism, its clinical importance is clear as proteinuria is very strongly associated with cardiovascular risk and progression of CKD at all levels of GFR [87, 88].

Even in the absence of evidence of CKD at 90 days, survivors of significant AKI should have at least one further check for CKD criteria at 1 year to check for late progression. A recent single-centre study examined patients who had eGFR greater than 60 mL/min/1.73 m^2 12 months or later after an episode of dialysis-treated AKI with a primary outcome of time to CKD as defined by eGFR persistently less than 60 mL/min/1.73 m^2 [95]. Interestingly, in this cohort few patients with no CKD criteria function at 1 year developed CKD over a median 9 years of follow-up. In those who did risk factors for the development of long-term renal impairment consisted of older age, diabetes and known vascular disease. Thus, it may be reasonable to assume that AKI survivors without CKD at 1 year after illness are at low risk in the absence of other risk factors.

As the long-term ill effects of AKI are partially mediated through the development of CKD the management of these patients should follow general current well-developed clinical CKD guidelines [96]. Treatment of hypertension and modification of cardiovascular risk factors are central to management of patients with or at risk of CKD. In patients with diabetes or proteinuria, angiotensin converting enzyme (ACE) inhibitors or angiotensin-2 receptor blocking agents should be first-line drugs for hypertension, as these may reduce proteinuria and the rate of progression of CKD [97]. However, recurrent episodes of AKI are a concern, and any follow-up programme should address the prevention and early detection of new episodes of AKI, including the need for early assessment with new acute illness and advice regarding the avoidance of nephrotoxin exposure and adjustment of regular medication in the setting of illness [98].

Conclusion

The acceptance of a unifying definition of AKI has increased awareness of the syndrome and generated much knowledge on morbidity and outcome. Less attention has been given to recovery from AKI. Despite many limitations, non-recovery of AKI is best defined as the presence of AKI criteria, and partial recovery as a fall in AKI stage. Both are associated with the development of CKD and cardiovascular diseases, need of chronic dialysis and mortality. The incidence of non-recovery differs between studies and populations. Risk factors include high age, CKD, comorbidity, higher severity of AKI and acute disease. After an episode of AKI serial follow-up measurements of serum creatinine and proteinuria are warranted to diagnose progressive renal impairment and implement measures to manage CKD if necessary.

Author details

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Compliance with ethical standards

Conflicts of interest

All authors declare that they have no conflict of interest.

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