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Points of Concern in Post Acute Kidney Injury Management

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Acute kidney injury · Renal recovery · Post acute kidney injury care · Chronic kidney disease · Referral · Quality improvement · Outcome

Abstract
The incidence of acute kidney injury (AKI) will in the future remain high, partly due to an increase in comorbidities and other AKI favoring factors such as the rise in high-risk diagnostic and therapeutic interventions. AKI has emerged as a major public health concern with high human and financial costs. It has recently been demonstrated that patients surviving an AKI episode show increased all-cause mortality, chronic kidney disease (CKD), ESRD, cardiovascular events, and reduced quality of life. Although it is important to acknowledge that, after an AKI episode, the risk of dying by far exceeds the risk of developing incident or progressive CKD and/or entering a maintenance renal replacement therapy (RRT) program, currently only a minority of patients are referred for renal follow-up, even after AKI-requiring RRT. On the other hand, renal follow-up for all AKI survivors might not be necessary and would represent an overwhelming work load for the health care system. There are at present no clear guidelines on which patients should be referred and on the elements of post AKI care that may improve non-renal and renal outcomes. In this review, we discuss several points of concern in post-AKI management and propose an algorithm on post-AKI care, mainly based on the renal recovery pattern at discharge from the hospital. Potential opportunities to improve care include appropriate risk stratification, close monitoring of kidney function, management of CKD complications, blood pressure control, medication reconciliation, and education of patients and non-nephrologists on AKI and its downstream complications.

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Introduction

Compelling evidence indicates that the global burden of acute kidney injury (AKI) has tremendously increased over the last years [1, 2]. This increase is partly attributable to an earlier recognition of the condition due to the use of lower thresholds in the diagnostic classification criteria. However, ageing of the general population, the increasing incidence of comorbidities, like diabetes mellitus, heart failure and sepsis, the rise in use of high-risk

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diagnostic and therapeutic interventions, and the exposure to nephrotoxic agents also contribute to the increased AKI incidence [3].

In high income countries, the incidence of hospital-acquired AKI exceeds that of community-acquired AKI by 5- to 10-fold, with a reported yearly incidence of 7–18% of hospital inpatients [1, 4].

Several observational studies have shown that survival of even mild episodes of AKI is associated with an increased risk of both short- and long-term mortality [5–9]. In addition, AKI in both non-dialysis and dialysis-requiring populations is associated with additional high costs compared to non-AKI populations [10].

It is also widely recognized that patients who survive an AKI episode are at considerable risk for developing de novo chronic kidney disease (CKD), progression of pre-existing CKD, and evolution towards end stage kidney disease.

The awareness of the increased risk for dismal outcome across different degrees of AKI severity, has stimulated interest in the follow-up and care of AKI survivors, mainly with the goal to screen for and to slow down CKD progression. Until now, there is no firm evidence that such follow-up care will improve the outcome, let alone be cost-effective [11]. Evidence-based guidelines on the organization of this care are not available.

This review intends to highlight specific concerns in the management of the post-AKI patient and to suggest a concrete proposal for the organization of post-AKI care.

Defining AKI and AKI Recovery

The introduction of the RIFLE, AKIN, and KDIGO classification criteria for AKI diagnosis, have brought uniformity to the diagnostic criteria, allowing comparison between studies and populations [12]. The majority of early studies on epidemiology and prognosis of AKI relied on diagnoses in administrative data sets, which are known to be variably applied and inherently biased toward more severe cases of AKI [13].

The KDIGO criteria classify patients according to changes in serum creatinine (sCr) and urine output (UO) by acknowledging the importance of small sCr increases and small decreases in UO within a certain time frame. As discussed by Kellum et al. [14], both sCr and UO criteria are important and the use of the KDIGO definition without assessment of UO underestimates the incidence of AKI and can delay diagnosis.

First, it is well known that acute changes in GFR may not be reflected by the sCr due to the time required for creatinine to accumulate and equilibrate. In addition, administration and retention of fluids will dilute sCr and in critically ill patients, due to inflammation-induced muscular wasting, the production of creatinine may be decreased. Critical illness is associated with a significant fall in sCr that persists to hospital discharge, potentially causing overestimation of the estimated GFR at discharge [15]. Taking these considerations into account, some modifications of the AKI definition based on sCr kinetics have been proposed [16] and applied in at least 2 clinical studies [17, 18]. Chen [19] suggested the use of kinetic estimated glomerular filtration ratio (eGFR) to assess the trajectory of renal function in the acute setting, when sCr values are still changing. The kinetic eGFR is calculated with a formula that is derived from the initial creatinine content, the distribution volume and production rate of creatinine and the quantitative difference between consecutive plasma creatinine values over a given time.

Second, absence of baseline values can lead to underestimation of recovery by misclassifying CKD as AKI. In a recent review, Siew and Matheny [20] discuss different approaches to select reference creatinine values and their relative merits and limitations. The authors conclude that the outpatient sCr measured within a year prior to the AKI hospitalization most closely approximates the baseline sCr value.

There is currently great interest for incorporating sCr trajectories into the creatinine classification criteria, which would eliminate the need for a baseline sCr value [21–23]. Analysis of sCr trajectories provides the opportunity to develop AKI staging based on the profile of sCr changes over time [22, 23]. In addition, Bhatraju et al. [21] demonstrated that the trajectory of sCr defines subphenotypes of AKI that are independently associated with hospital mortality, length of hospital stay, and length of ICU stay. Critically ill patients with a non-resolving AKI subphenotype had a greater than 60% increased risk of hospital mortality compared with no renal dysfunction or patients with a resolving subphenotype.

Third, the currently used AKI classification criteria do not consider the primary etiological diagnosis. It can be assumed that the same degree of creatinine increase may portend a different prognosis according to the underlying etiology of the AKI episode. It should also be reminded that the KDIGO staging of AKI which is based on UO and/or sCr is defined by the worst level that is achieved with one or both of these parameters. However, the same stage can be associated with a different prognosis according to whether the worst criterion is based on UO, sCr, or both [14].

Fourth, there is no consensus on how to define AKI recovery and degree of AKI recovery. Varying definitions of renal recovery (complete, partial, and/or non-recovery) after AKI have been applied over the last years [24]. KDIGO also introduces the concept of acute kidney disease (AKD) defined as acute or subacute damage and/or loss of kidney function for a duration of between 7 days and 3 months after exposure to an AKI initiating event. Since by definition CKD starts after 3 months, AKD patients do not yet fulfill the criteria for diagnosis of CKD.

The ideal definition of recovery should be based on pre-existing as well as current residual kidney function but the practical approach should also take in to account possible loss of kidney function at baseline. In addition, the definition should identify when recovery is complete and should provide prognostic information. It is crucial that both the timing and return to baseline kidney function are considered in the definition of recovery [25], taking into consideration that there is a non-linear clinical course post AKI with risk prediction dependent on the time point at which risk is assessed [26]. Detailed information on definitions of AKI, AKD, and CKD, staging criteria for AKD, renal recovery, and strategies for the management of affected patients can be found in the most recently published ADQI 16 Workgroup Report [27].

Role of Novel Biomarkers in Predicting Long-Term Post AKI Outcome

Extensive efforts were spent over the last 15 years to identify and validate novel biomarkers in AKI that are more sensitive for onset of injury, and with greater discrimination for injury severity than the classical markers like sCr and/or Cystatin C and/or UO.

Data linking biomarkers to long-term outcomes including CKD and mortality are scarce [28].

Older studies, collectively summarized by Koraishy and Coca [29], suggest that several biomarkers related to AKI might be useful to determine which patients with AKI have a high likelihood for recovery. In unselected ICU patients with severe AKI, it seems that multiple biomarkers will need to be combined with clinical variables to achieve excellent accuracy at predicting recovery [29].

More recently, a cross-sectional evaluation for signs of chronic kidney injury using both traditional measures and novel urinary biomarkers was performed in a pediatric population with and without AKI post-cardiac surgery [30]. It appeared that urinary biomarker levels (interleukin-18 [IL-18], kidney injury molecule 1 [KIM-1], and liver fatty acid binding protein [L-FABP]) remain elevated 7 years after an episode of AKI despite absence of conventional evidence of CKD. Although the significance of these findings remains unclear, it suggests that "subclinical" kidney injury and/or inflammation may still continue even after apparent functional recovery of AKI. On the other hand, the recently published Chronic Renal Insufficiency Cohort Study shows that among patients with CKD, risk prediction with a clinical model that includes the sCr-based eGFR and the urinary albumin/creatinine ratio is not improved with the addition of renal tubular injury biomarkers, including KIM-1, NGAL, N-acetyl-b-D-glucosaminidase, and L-FABP [31]. Furthermore, a recent multicenter cohort study of adults undergoing cardiac surgery found that severity and duration of postoperative creatinine-defined AKI were strongly associated with cardiovascular events and mortality; however, peak postoperative elevations in urinary kidney injury biomarkers (IL-18, NGAL, KIM-1, L-FABP, and albumin) were not significantly associated with increased risk after adjusting for confounders. In contrast, the peak cardiac injury biomarkers (NT-proBNP, H-FABP, hs-cTnT, cTnI, and CK-MB) explained approximately half of the association between clinical AKI and the primary composite outcome of cardiovascular events and mortality [32].

Larger, well-designed studies need to validate the ability for biomarkers to predict recovery from severe AKI and its prognosis.

AKI-CKD Link: Potential Confounders

Although recent literature provides a strong base for the AKI-CKD link, there is still controversy on the causality of this association. As recently pointed out by Coca [33] much of the previous literature has not been sufficiently stringent in identifying the extent by which CKD after AKI results from an irreversible fixed defect due to non-recovery from tubular injury, manifesting as a steep drop and plateau of renal function at a new baseline versus de novo progression of AKI.

First, AKI and CKD share a number of common risk factors making it difficult to conclude with certainty that AKI is causally related to CKD. Moreover, a systematic review [26] including 7,385 citations, found only 30 studies that met the preset quality criteria for selecting patients with AKI with sufficient efforts to avoid misclassifying CKD. Especially in large databases, where historical baseline sCr values are often unknown or inaccurate and

sometimes unreliable administrative codes are used [13], there is a risk for misclassification of AKI and CKD. A baseline function is required for grading AKI severity, as a reference for establishing if recovery is complete and as a means of stratifying patients with and without CKD existing pre-AKI. Evidently, misclassification will confound the association between AKI and CKD.

Second, recovery of renal function may take on multiple trajectories [24]. Progression of CKD may be complicated by unpredictable, possibly random and even subclinical episodes of usually self-limited AKI which makes the correct interpretation of the rate of progression difficult [34]. A patient with a non-progressive or slowly progressive trajectory may have a clinical event resulting in AKI, which not only abruptly drops the GFR off the projected trajectory, but due to a critical loss of nephron mass, may also change the future trajectory starting from the new baseline GFR. In a follow-up study from our unit, considering only patients with known CKD, progression of CKD was essentially defined by episodes of AKI and the incomplete recovery of kidney function after each acute event [35].

Third, many factors such as severity of AKI [36], duration of AKI [37], the (controversial) issue of choice of initial renal replacement therapy (RRT) modality [38], cause of AKI, and degree of recovery of AKI at a certain time point after AKI [26, 36] influence the relationship between AKI and CKD, which might be different across different strata of the aforementioned variables. The clinical course as well as the risk for CKD might vary by time. Several studies do not consider the degree of AKI recovery at a certain time point in the assessment of later CKD development or CKD progression. However, while the severity of AKI is important in late outcome, it is actually the amount of residual renal function present on discharge that is the factor better associated with outcome [39]. Table 1 summarizes some recent studies assessing CKD outcome in relation to AKI recovery. Of note, all of these studies were retrospective. Important heterogeneity in definitions of AKI, of recovery and of CKD outcome are noted in the different studies.

A recent small but prospective single-center cohort study also found that AKI is associated with deterioration in renal function after 3 years, even in an unselected population with predominantly AKI stage 1. Non-recovery from AKI turned out to be an important factor determining negative long-term outcome [40].

A recent analysis [41] studied the long-term (10 years) trajectory of subsequent renal decline in post-AKI survivors and used the 1 year post-discharge eGFR rather than the pre-admission value as a new reference point. Outcomes were sustained 30% renal decline and de novo CKD stage 4. Death was more common than subsequent 30% renal decline (37.5 vs. 11.3%) and CKD stage 4 (4.5%). Overall, 25.7% of AKI patients had non-recovery. The increased risk from AKI (vs. no AKI) was greatest (more than 2-fold) among those who experienced recovery to normal levels (eGFR ≥60 mL/min/1.73 m^2), even when those with post-episode proteinuria were excluded (for more details, see reference [39]; Table 1).

Studies analyzing the AKI-CKD link should address pre-AKI baseline kidney function, degree of post-AKI recovery at well-defined time points and use a non-AKI group with similar severity of illness as comparator.

It is likely that the risk for poor late outcome is not the same across different settings and AKI etiologies, independent of AKI severity, duration, and degree of recovery. Studies should distinguish between community-acquired and hospital-acquired AKI and AKI occurring in the critically ill setting. It is not surprising that the outcome of, for example, acute allergic interstitial nephritis is different compared to AKI in a critically ill diabetic post-cardiac surgery patient. In the critically ill with AKI requiring acute renal replacement therapy (AKI-RRT), several factors are associated with recovery such as younger age, male sex, low burden of comorbidities, normal baseline renal function, presence of severe sepsis/septic shock, and lower sCr value at the moment of RRT initiation [42].

It can be anticipated that referring all patients who suffered from an AKI episode for follow-up care to a nephrology clinic would create an overwhelming burden to the nephrology community. It is thus imperative to select those patients who are at the highest risk for bad outcome for specific post-AKI care.

Post-AKI Care: Who and How?

Current reality is that patients are rarely seen by a nephrologist after an AKI episode even in AKI-RRT. Siew et al. [43] calculated that within the first year after an episode of AKI-RRT the cumulative incidence of nephrology referral was only 8.5% among survivors who were considered to be at risk for subsequent decline in kidney function. Severity of AKI did not affect referral rates. There is at present not much convincing evidence whether early nephrology involvement has a beneficial impact on the long-term outcome of the post-AKI patient. Harel et al. [44] found that the value of nephrology follow-up is

Table 1. Main studies on risk of CKD according to recovery status post AKI

Author/study design	Setting/number of patients	AKI definition	AKI recovery: definition/ timing or pattern	CKD outcome	Results
van Kuijk et al., 2010/ retrospective cohort [60]	Patients who were referred for elective major vascular surgery between 1990 and 2008 and with eGFR >60 mL/ min/1.73 m^2/AKI n = 493, no AKI n = 815	sCr was measured at baseline in all patients and at day 1 or 2 and day 3 after surgery. Patients were categorized into 3 groups on the basis of changes in CKD-EPI from baseline to day 1 or 2 and from day 1 or 2–day 3 Group 1: unchanged or improved renal function (change in GFR -10–10% compared with baseline); group 2: temporary decline of renal function (>10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3); group 3: persistent decline renal function (>10% decrease compared with baseline)	Group 1: unchanged or improved renal function (change in GFR-10–10% compared with baseline); group 2: temporary decline of renal function (>10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3); group 3: persistent decline renal function (>10% decrease compared with baseline)	Development of incident CKD eGFR <60 mL/ min/1.73 m^2 and at least 25% decrease from baseline Median follow-up time: 5 years (IQR 2.6–8.5)	RR for CKD development – No change: RR 1.0 (reference) – Temporary decline: 3.4 (2.7–4.1) – Persistent decline: 3.6 (2.8–4.4) Sensitivity analysis with different cut-off values and "no change" group as reference: 20% – Temporary decline: 3.5 (2.8–4.2) – Persistent decline: 4.2 (3.2–5.2) 30% – Temporary decline: 3.5 (2.8–4.2) – Persistent decline: 4.3 (3.3–5.4) 40% – Temporary decline: 3.6 (2.9–4.3) – Persistent decline: 3.9 (2.8–5.1) 50% – Temporary decline: 3.8 (2.9–4.3) – Persistent decline: 3.9 (2.8–5.1)
Wu et al., 2011/ retrospective cohort [61]	Patients admitted to ICU for >2 days after major surgery between January 2002 and January 2008 (database of the National Taiwan University Hospital Study Group on Acute Renal Failure) AKI n = 4393, no AKI n = ICU after major surgery	AKI according to RIFLE based on the sCr criterion Acute on chronic: sCr increase >50% or eGFR decrease of >25% in patients with baseline eGFR ≤45 mL/ min/1.73 m^2	Recovery = discharge sCr <50% above baseline sCr Non-recovery: persistent increase in sCr > 50% above baseline sCr or need for RRT Median follow-up time: 4.62 years	Long term dialysis dependence	HR for RRT dependence Non-CKD-non-AKI: 1.0 (reference- CKD without recovery: HR 212.73 (105.53–428.83) CKD with recovery: HR 74.07 (38.82–141.32) Non-CKD without recovery: HR 60.95 (24.13–153.97) CKD-non AKI: HR 42.63 (20.82–87.29) Non-CKD with recovery: HR 4.5 (2.43–8.35)
Jones et al., 2012/ retrospective cohort [62]	Patients hospitalized between January 1999 and December 2009 (Intermountain Healthcare Enterprise Data Warehouse) with eGFR >60 mL/min/1.73 m^2/ AKI n = 719, no AKI n = 3,090	ICD9 codes for AKI and AKIN based on the sCr criterion	Complete recovery = return of sCr to a level less than 1.10 (10%) times the baseline sCr within 7 days of the discharge date Additional analyses for different definitions of recovery: a return of the sCr to a level less than 1.25 (25%) and 1.5 (50%) times the baseline sCr Median follow-up time: 2.5 years (25th P:1.1 years, 75th P: 5.3 years)	Incident CKD stage 3 defined as eGFR <60 mL/ min/1.73 m^2 that persisted for at least 3 months prior to the end of follow-up	HR for incident CKD – Complete recovery within 10%: HR 3.82 (2.81–5.19) – Complete recovery within 25%: HR 3.87 (2.87–5.21) – Complete recovery within 50%: HR 4.21 (3.17–5.60)

Table 1. (continued)

Author/study design	Setting/number of patients	AKI definition	AKI recovery: definition/ timing or pattern	CKD outcome	Results
Bucaloiu et al., 2012/ retrospective propensity score-matched cohort [56]	Patients discharged from Geisinger Medical Center, Pennsylvania (study data source: Geisinger's electronic health record, EpicCare) with eGFR >60 mL/min/1.73 m^2 and no proteinuria/AKI n = 1,610, no AKI n = 3,652	50% increase in sCr compared to baseline value occurring during hospitalization	eGFR within at least 90% of baseline eGFR occurring within 90 days of AKI	Development of CKD defined as the occurrence of 2 or more eGFR values ≤59 mL/ min/1.73 m^2, separated in time by at least 90 but no more than 365 days	The incident rates for CKD were 28.1 and 13.1/1,000 person years in the AKI and control groups, respectively; the corresponding CKD ratio was 2.14 (1.96–2.43) HR for de novo CKD in recovered AKI versus controls: 1.91 (1.75–2.09)
Pannu et al., 2013/ retrospective cohort [63]	Participants identified from a provincial claims registry in Alberta, Canada, hospitalized between November 2002 and December 2007 and baseline eGFR >15 mL/min/1.73 m^2/ AKI n = 4,111, no AKI n = 155,090 Alberta registry, hospitalized adult patients	2-fold increase in sCr between prehospital and peak in-hospital value and/or RRT need	Recovery was assessed using sCr drawn closest to 90 days after the AKI event; recovery = return to within 25% of baseline sCr and independence of RRT Sensitivity analysis: different definitions of AKI recovery with reference group those who recovered within 5% of baseline, with 10% increments for each level of recovery until 55%	Composite outcome of sustained doubling of sCr or ESRD requiring RRT Median follow-up time: 34 months (0.13–74); 25th P: 20 months, 75th P: 50 months	2.1% AKI survivors progressed to ESRD and 9.9% had a sustained doubling of sCr versus 0.4% and 2.8% in the non AKI group HR for CKD outcome AKI recovered: HR 1 (reference) AKI non recovered: 4.13 (3.38–5.04) Sensitivity analysis: relative to the participants who recovered within 5% of baseline sCr, the cut-off point at which a significant difference in renal survival was observed was when recovery was defined as within 25–35% of baseline
Heung et al., 2016/ retrospective cohort [36]	Patients from the US Veterans Health Administration, hospitalized in 2011 for >24 h with at least 2 inpatients sCr measurements and baseline eGFR >60 mL/min/1,73 m^2/ AKI n = 17,049, no AKI n = 87,715	KDIGO according to creatinine criterion	Recovery to creatinine level within 0.3 mg/dL of baseline/fast recovery: within 2 days of peak inpatient sCr level; intermediate recovery: recovery in 3–10 days from peak; slow or no recovery: sCr still elevated above baseline at 10 days after peak inpatient Scr;	CKD stage 3 or higher by 1 year post discharge from the index hospitalization	RR for CKD outcome AKI stage 1 – No AKI: 1.00 (reference) – Full recovery: 1.43 (1.39–1.48) – Intermediate recovery: 2.00 (1.88–2.12) – No or slow recovery: 2.65 (2.51–2.80) AKI stage 2 – No AKI: 1.00 (reference) – Full recovery:1.80 (1.46–2.23) – Intermediate recovery: 1.91 (1.49–2.45) – No or slow recovery: 3.31 (2.85–3.84) AKI stage 3 – No AKI: 1.00 (reference) – full recovery: 1.96 (1.64–2.34) -intermediate recovery: 2.20 (1.91–2.53) -no or slow recovery: 3.59 (3.27–3.94)

Table 1. (continued)

Author/study design	Setting/number of patients	AKI definition	AKI recovery: definition/timing or pattern	CKD outcome	Results
Sawhney et al., 2017/ retrospective cohort [41]	Hospital survivors (Grampian resident adult population) in 2003 with eGFR ≥30 mL/min/1.73 m^2 at 1 year after discharge/AKI n = 1,966, no AKI n = 12,685	KDIGO based on the sCr criterion	Follow-up time between 2003 and 2013	Sustained 30% renal decline and de novo CKD stage 4	HR for sustained 30% renal decline – eGFR ≥60 mL/min/1.73 m^2: HR 2.29 (1.88–2.78) – eGFR 45–59 mL/min/1.73 m^2: HR 1.50 (1.13–2.00) – eGFR 30–44 mL/min/1.73 m^2: HR 0.94 (0.68–1.32) – eGFR <30 mL/min/1.73 m^2: HR 0.95 (0.64–1.41) HR for de novo CKD 4 – eGFR ≥60 mL/min/1.73 m^2: HR 2.36 (1.31–4.24) – eGFR 45–59 mL/min/1.73 m^2: HR 1.55 (1.02–2.34) – eGFR 30–44 mL/min/1.73 m^2: HR 1.08 (0.85–1.38)

AKI, acute kidney injury; AKIN, acute kidney injury network; CKD, chronic kidney disease; (e)GFR; (estimated) glomerular filtration ratio; ICD9, 9th version of the international statistical classification of diseases and related health problems; KDIGO, kidney disease improving global outcomes; RIFLE, risk injury failure loss of kidney function and end stage renal disease; RR, relative risk; RRT, renal replacement therapy; sCr, serum creatinine.

most pronounced in patients with de novo renal disease as they may benefit from early management of CKD and its complications. In contrast, patients who were already followed by a nephrologist before their hospitalization for AKI had a higher mortality compared to patients followed by either general practitioners, cardiologists or internists. It can be speculated that those patients may already have had underlying multisystem injury from their longstanding renal disease and its complications, and that therefore the benefit of post-AKI nephrology follow-up is attenuated.

It should be acknowledged that following an episode of AKI, the balance of the risks of mortality and those of subsequent CKD remains uncertain. In 2009, Wald et al. [45] concluded that AKI-RRT was associated with an increased risk of chronic dialysis but not with an increase in all-cause mortality and a systematic review reported that absolute rates of CKD following AKI were approximately 50% higher than that for mortality [46]. In contrast, recent studies found that both in AKI-RRT and AKI-non RRT, the risk of dying exceeds the risk of entering a maintenance dialysis program [41] The causes of death in these patients are mainly cardiovascular in nature [5, 7–9, 47].

The most recent and largest study of early prognosis of post AKI surviving patients, included a cohort of 156,690 patients and described that over the 30 days post-discharge, 18% patients were readmitted to the hospital, 10% visited the emergency department without being admitted to the hospital, and 5% patients died without incurring a hospitalization or emergency department visit. In this study, the overall mortality rate at 30 days for the entire cohort was 8%. The 5 most common primary hospital readmission diagnoses were heart failure (13%), recurrent AKI (6%), chronic obstructive pulmonary disease (3%), palliation (3%), and urinary tract infection (3%) [48].

Also unplanned post AKI readmission rates usually within 30–90 days are high [49] and are mainly due to pulmonary edema [50].

The weeks after hospital discharge from AKI, are therefore critical. Some patients may still have ongoing illness, some may be vulnerable to recurrent insults and some may have modifiable risk factors that have been overlooked [51].

The analysis of the major reasons of post-discharge mortality and early readmission rates of the surviving AKI patients is of relevance for the organization of the post-AKI care and the referral pattern of these patients. Although very important, nephrologic follow-up alone

will often not be sufficient and a multi-disciplinary patient-centered approach addressing the still ongoing illness of the patient is needed.

Whatever the mortality associated with AKI, a substantial number of post-AKI survivors are at risk for either de novo CKD or progression of preexisting CKD. Since the 2004 landmark paper by Go et al. [52], nephrologists are well aware about the increased burden of cardiovascular diseases complicating advanced stages of CKD. Nephrologists should thus be more skilled in recognizing and managing these complications in the post-AKI patient with de novo or progressive pre-existing CKD. The treatment of hypertension and proteinuria, the avoidance of nephrotoxins, and the prevention and treatment of the many metabolic complications of the CKD patient are among the core elements of care provided by nephrology clinics.

Silver et al. [53, 54] established a post-AKI clinic in 2 tertiary hospitals in Toronto where all patients are seen 30–90 days after hospital discharge following an AKI episode. Such clinics might not only expose previously unrecognized CKD but also deliver appropriate prevention and treatment of CKD and its complications, avoiding early readmissions [48]. These clinics can also create the opportunity for educating patients, primary care providers and non-nephrology specialists on AKI and its downstream complications. An additional advantage of a structured post AKI follow up is to install care bundles and guidelines on AKI at the hospital level. Finally, although an exact quantification of the extra costs associated with post-discharge AKI care is not available [10], it can be expected that better organization of this care will reduce these extra costs.

Proposal for Clinical Follow-Up of Post-AKI Patients (Fig. 1)

Any episode of AKI should at discharge be formally documented in the medical record. In one study [55], formal documentation occurred in only 43% of patients with AKI and after adjustment for severity of disease, documentation was associated with reduced 30-day mortality.

High risk patients (severe AKI [KDIGO ≥ stage 2/RRT need], AKI in transplant recipients, or, irrespective of the degree of AKI, age above 65 years, or comorbidities like hypertension, diabetes mellitus, cardiovascular disease, liver cirrhosis, and those actively treated for cancer) should before discharge be seen by a nephrologist and educated about AKI, the prevention of further AKI episodes, and the importance of follow-up.

Figure 1 summarizes a suggestion of an algorithm on post AKI renal follow-up, based on the scarce available literature [53, 54].

We suggest that post-AKI patients at high risk for de novo or progressive CKD are first evaluated for degree of recovery at the moment of hospital discharge. In our algorithm, we choose to define "complete recovery at discharge" by an eGFR within 90% of the baseline eGFR. The criterion of a 90% reduction is a modification of the suggestion of Bucaloiu et al. [56] who evaluated the risk of de novo CKD post AKI, based on an eGFR at 3 months post discharge. We realize that at discharge, the majority of AKI patients might not yet be in steady state. Theoretically, measuring a short term (e.g., 4 h) endogenous creatinine clearance or ideally a true GFR via inulin clearance at discharge would be preferable. However, both methods are either unpractical and/or expensive and are thus rarely performed. In case the baseline eGFR is not available, we suggest to use the admission eGFR as a surrogate comparator. When eGFR at discharge is within 90% of a subnormal admission eGFR we assume that it is most likely that the patient has CKD.

We define "incomplete recovery" when the eGFR is not within 90% of the baseline eGFR. Incomplete recovery also includes those patients for whom the baseline eGFR is not available and where at discharge the eGFR is less than 90% of the admission eGFR. These patients probably have suffered or still suffer from either AKI (within 7 days), AKD (longer than 7 days), or acute on underlying CKD.

Patients with complete recovery at discharge can be referred to a post-AKI clinic after 3 months. Patients with incomplete recovery are referred to the post-AKI clinic either after 3 weeks or earlier, depending on the clinical context. In both groups the eGFR is calculated at 3 months. When the eGFR is below 60 mL/min/1.73 m^2, these patients should be directly referred to the outpatient ambulatory nephrology clinic. When the eGFR is above 60 mL/min/1.73 m^2 the follow-up is determined by the relative decrease in eGFR. When the decrease is less than 25%, patients can be referred to primary care with clear instructions for follow-up. When on the other hand, the decrease is more than 25%, these patients should be seen at the post AKI clinic at 6 and 12 months. When during this follow-up the eGFR drops below 60 mL/min/1.73 m^2, these patients should again be referred to the outpatient ambulatory nephrology clinic (Fig. 1).

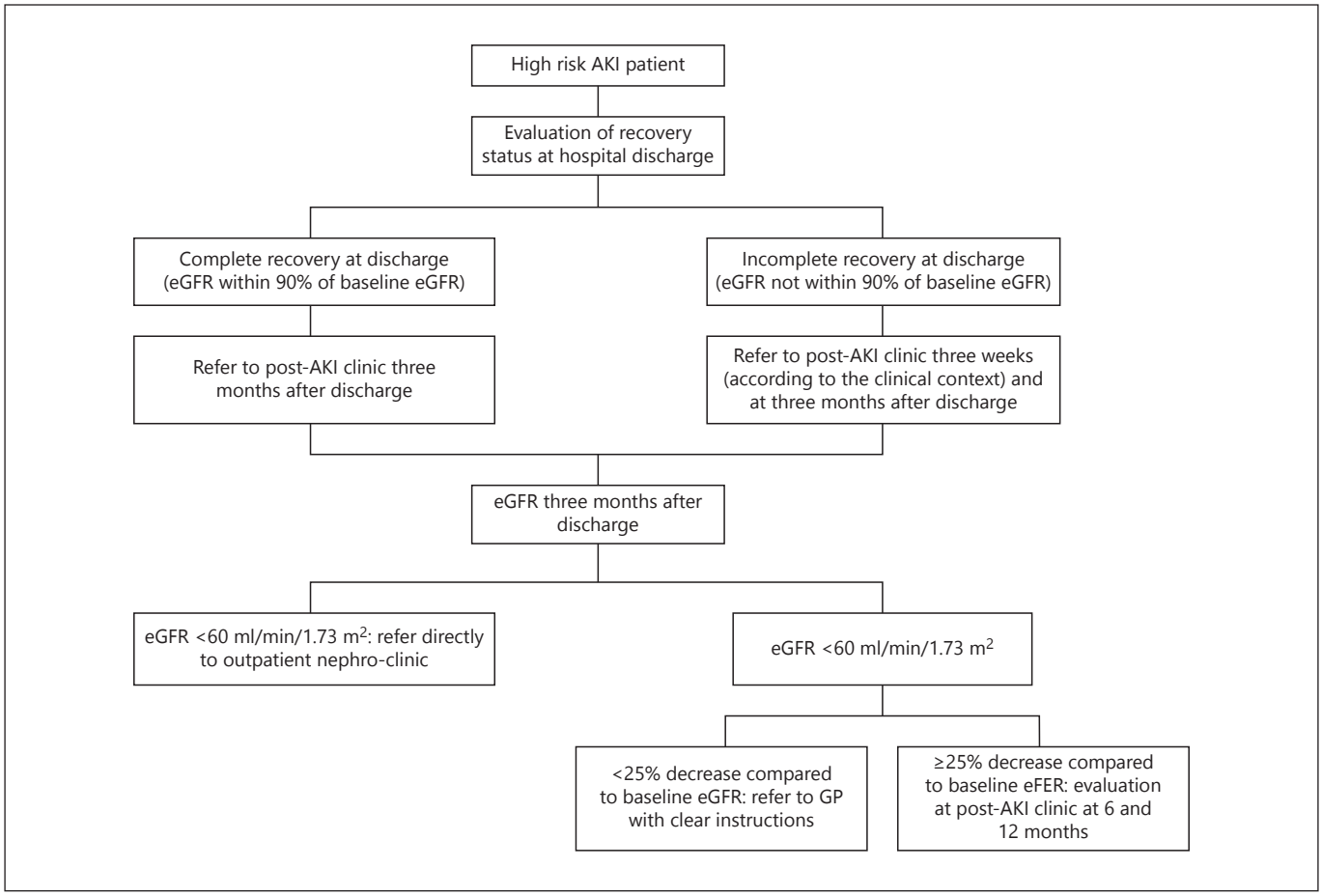

Fig. 1. An example of a possible algorithm for renal follow-up after AKI in high risk patients (see text for definition of high risk patients and further explanation of the algorithm). AKI, acute kidney injury; eGFR, estimated glomerular filtration ratio; GP, general practitioner.

At each medical follow-up visit, the adherence to a "minimal" renal care bundle should be respected. This bundle includes attention to obvious parameters (blood pressure, body weight, sCr, eGFR, and urinary protein/albumin to creatinine ratio). De nova proteinuria should be treated.

A "medicines sick day rules" card could be provided to patients and they should receive clear face-to-face instructions on which potentially nephrotoxic drugs should be temporarily withheld under which conditions [57]. Table 2 summarizes selected recommendations on medication management.

Although recovery of AKI can take as long as 18 months [58] after the initial episode, most AKI patients recover earlier. However, the recent results described by Sawhney et al. [41] should remind us that even if post-discharge kidney function returns to normal, any hospital admission with AKI is associated with increased risk of renal progression that may persist for up to 10 years, so that complete reassurance can never be provided. There is thus no clear recommendation on the duration that AKI survivors should be monitored after the AKI episode for evaluation of CKD development; some guidelines suggest a follow up for 2–3 years (NICE CKD guidelines) even if there is a return to baseline function [59].

Conclusion

There is a potentially causal association between AKI and increased risk for de novo CKD, or progression of CKD and end stage kidney disease, but the risk of death is more pronounced. Although there is no hard evidence that involving a nephrologist in post AKI man-

Table 2. Post-AKI medication management

Restart appropriate medications that may have been stopped during the AKI episode	
Antihypertensives, anticoagulants, anti-aggregants	Antihypertensives are often stopped but need restarting when blood pressure rises during recovery
	iACEi/ARB can be restarted (unless specific advice to the contrary) once the renal function has stabilized – sCr should be checked 1 week after reintroduction
	If aspirin (75 mg once daily) and statins were stopped, these should be restarted unless specific contra-indications. Aspirin 75 mg is not nephrotoxic
If a drug is specifically implicated in causing AKI, e.g., proton pump inhibitors (PPI) leading to interstitial nephritis or non steroidal anti inflammatory drugs (NSAIDs), practice records should be updated to prevent the patient receiving these in future	
Adapt drug dosing according to the post-AKI kidney function	

agement is beneficial, there are reasons to believe that he/she is best suited for this task and that organizing post-AKI care might have a positive impact on patient outcome. High risk patients could be referred to a post-AKI clinic for a duration of up to one year, with further triage down the line and referral to the GP or the outpatient nephrology clinic, according to the eGFR. Patients and caregivers other than nephrologists should be educated about the health risks associated with an AKI episode even in case of initial complete recovery of kidney function.

Disclosure Statement

The authors declare no conflicts of interest.

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