CURRENT OPINION

Improving outcomes of acute kidney injury survivors

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Purpose of review
Acute kidney injury (AKI) is a common problem in critically ill patients, with long-term health implications that extend beyond hospital discharge. Though they are at a high risk of adverse events, AKI survivors may not be receiving adequate postdischarge medical attention. This review discusses recently published data regarding health outcomes after AKI, the current state of post-AKI care, and potential opportunities to improve outpatient care after AKI.

Recent findings
In addition to predisposing to de-novo chronic kidney disease or an exacerbation of previously existing chronic kidney disease, a prior episode of AKI has been linked to subsequent cardiac events, cerebrovascular events, and the need for hospital readmission. Despite this, a population-wide study in Ontario showed that only 40% of patients surviving an episode of dialysis-requiring AKI visited a nephrologist within 90 days of hospital discharge. This care gap is important since outpatient contact with a nephrologist during this critical period was associated with enhanced survival.

Summary
AKI is associated with a number of long-term health effects, and new strategies may be needed to address this emerging public health issue. An ambulatory program dedicated to the postdischarge care of AKI survivors may confer a variety of benefits. Future research is needed to evaluate this model of care.

Keywords
acute kidney injury, chronic kidney disease, quality improvement, transitions in care

INTRODUCTION

Acute kidney injury (AKI) is a common problem in critically ill patients and complicates 30–40% of critical care admissions [1▪,2▪]. Although the in-hospital morbidity and mortality associated with AKI is well documented, the relationship between hospital-associated AKI and postdischarge morbidity and mortality is garnering increased recognition. With the incidence of AKI estimated to increase in the coming years, the long-term consequences of an AKI episode may have significant public health implications [1▪,3,4]. Nonetheless, a minority of AKI survivors receive comprehensive postdischarge care as afforded to other high-risk populations.

The review will demonstrate the long-term complications associated with a hospitalization for AKI, and possible gaps in the care provided to AKI survivors. We argue that AKI survivors represent a vulnerable population, and suggest some strategies to potentially improve their postdischarge care.

SURVIVAL AFTER HOSPITAL-ASSOCIATED ACUTE KIDNEY INJURY

Most epidemiologic studies have demonstrated an association between hospital-associated AKI and postdischarge mortality [5,6▪], which was demonstrated in a variety of contexts for AKI, including myocardial infarction (MI) [7–9], cardiac surgery [10], critical care [11], and general inpatients [12–15]. In a recent meta-analysis by Coca *et al.* [5], survivors of hospital-associated AKI had a pooled mortality rate of 16.8/100 person-years, which represented a two-fold adjusted risk of death compared with patients discharged from hospital

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Curr Opin Crit Care 2015, 21:500–505

DOI:10.1097/MCC.0000000000000261

KEY POINTS

- Patients who survive hospital-associated AKI are at an increased risk for kidney events, cardiovascular events, and rehospitalizations.
- Patients who survive an episode of AKI have worse outcomes than patients who survive an MI.
- A minority of patients discharged after an episode of severe hospital-associated AKI receive follow-up with a nephrologist, even though seeing a nephrologist within 90 days of hospital discharge has been associated with enhanced survival.
- AKI survivors represent a vulnerable population who may benefit from specialized postdischarge care to improve long-term outcomes.

who did not experience AKI. Recent work by Chawla *et al.* [16■■] further highlighted the sustained risk of death among AKI survivors. They studied the course of 36 980 US veterans following hospitalization for AKI, MI, or the combination of AKI and MI (AKI + MI). Median follow-up was 1.4 years after the index hospitalization. Compared with patients with an MI uncomplicated by AKI, patients with AKI and AKI + MI had a markedly higher risk of death [adjusted hazard ratio (HR) 1.85, 95% confidence interval (CI) 1.76–1.94 and 2.14, 95% CI 2.05–2.23, respectively].

There is limited information on the causes of death among AKI survivors. Follow-up of a 258-patient subset from the Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial (mean duration 3.5 years after entry into the trial) identified cancer (18%), ischemic heart disease (13%), sepsis (12%), pneumonia (10%), and congestive heart failure (8%) as the most common causes of death [17■].

KIDNEY OUTCOMES AFTER AN ACUTE KIDNEY INJURY HOSPITALIZATION

An episode of AKI has been strongly associated with de-novo chronic kidney disease (CKD) classically defined as an estimated glomerular filtration rate (eGFR) $< 60\,\mathrm{ml/min/1.73\,m^2}$ and progression of pre-existing CKD [18■■]. In the previously-cited meta-analysis, AKI survivors had pooled CKD rates of 25.8/100 person-years (HR 8.8, 95% CI 3.1–25.5 compared with patients without AKI) [5].

End-stage renal disease (ESRD), defined as the need for either chronic maintenance dialysis or a kidney transplant, is the most extreme form of CKD and has also been associated with prior episodes of AKI [19–21,22■]. Gammelager *et al.* [23■] used population-based registries in Denmark to identify 3062 patients who received dialysis for AKI and survived for 90 days after admission to a critical care unit. Median follow-up time was 3.1 years. At 180 days after ICU admission, ESRD was present in 8.5% with prior dialysis-requiring AKI compared with 0.1% for other critical care patients (adjusted HR 105.6, 95% CI 78.1–142.9). The cumulative risk of ESRD at 5 years among patients with dialysis-requiring AKI was 11.7% (95% CI 10.5–13.0).

Extended follow-up of the RENAL trial cohort demonstrated that among survivors to day 90, 5% of participants reached ESRD at 4 years [17■]. Albuminuria, a potentially modifiable marker of kidney damage, was observed in 42% of surviving patients. The presence of albuminuria is important because it is an independent risk factor for CKD progression, cardiovascular disease, and death [24].

Several other factors may increase the risk of CKD progression after an AKI episode. Recurrent AKI insults are more likely to confer irreversible damage [25]. The severity of the index AKI episode also appears to be particularly important, with the risk of both ESRD and CKD increasing in a graded manner with the severity of the initial insult [26].

A patient's residual kidney function at the time of hospital discharge also appears to be an important predictor of long-term outcomes. A retrospective study of 1500 cardiac surgery patients found that for each $88\,\mu\mathrm{mol/l}$ increase in creatinine at discharge, the HR for death was 1.90 (95% CI 1.54–2.34) [27■]. Stads *et al.* [28] demonstrated a similar finding among 1220 critically ill patients who received continuous renal replacement therapy for AKI. They found a graded relationship between eGFR at hospital discharge and both mortality and ESRD. The effect was most pronounced for patients with an eGFR below $30\,\mathrm{ml/min/1.73\,m^2}$ (HR for death = 1.62, 95% CI 1.01–2.58; HR for ESRD = 27.4, 95% CI 5.79–129.6) and $15\,\mathrm{ml/min/1.73\,m^2}$ (HR for death = 1.93, 95% CI 1.23–3.02; HR for ESRD = 176.9, 95% CI 38.59–811.5). Pannu *et al.* [29■] also found kidney function at hospital discharge to be an important predictor of adverse events. AKI survivors who did not recover kidney function had a higher risk for mortality and adverse kidney outcomes (composite of sustained doubling of serum creatinine or ESRD) than individuals who recovered to within 25% of their baseline serum creatinine (adjusted HR for mortality 1.26, 95% CI 1.10–1.43; adjusted HR for kidney outcomes 4.13, 95% CI 3.38–5.04).

Although impaired kidney function at hospital discharge is associated with a poor prognosis, dependence on serum creatinine-based estimates

Table 1. Risk factors for kidney disease progression after an acute kidney injury episode

Old age [26,27▪,31]
Higher Charlson Comorbidity Score [22▪,29▪,31]
Baseline CKD [22▪,28,29▪]
Diabetes [27▪,29▪]
Hypertension [22▪,31]
Heart failure [29▪,31]
Low serum albumin [26]
AKI severity [5]
Discharge serum creatinine [27▪,28,29▪]
Recurrent AKI episodes [25]

AKI, acute kidney injury; CKD, chronic kidney disease.

of kidney function might confound the actual residual glomerular filtration rate and obscure irreversible kidney damage that has occurred. After a prolonged critical illness associated with muscle wasting, the serum creatinine concentration could be depressed because of decreased production by muscle [30▪]. In patients with a baseline eGFR over 60 ml/min/1.73 m^2, Bucaloiu *et al.* [31] identified 1610 patients with hospital-associated AKI with apparently complete renal recovery within 90 days. These patients were matched to a control group of patients who did not experience AKI using a propensity score for the likelihood of developing AKI. After a median follow-up of 3 years, the rate of incident CKD was 28.1 cases/1000 person-years in AKI survivors and 13.1 cases/1000 person-years in patients without prior AKI. These findings suggest that AKI survivors are at risk for adverse kidney outcomes even if their kidney function, as defined by serum creatinine, appears to normalize by hospital discharge. Table 1 summarizes the different risk factors associated with adverse kidney outcome after an AKI episode.

CARDIOVASCULAR OUTCOMES AFTER AN ACUTE KIDNEY INJURY HOSPITALIZATION

Recent studies have highlighted a compelling relationship between AKI and cardiovascular events. Wu *et al.* [32▪▪] used a propensity score to match 4869 Taiwanese patients who became dialysis independent after an episode of dialysis-requiring AKI to individuals who did not have AKI. Patients with a prior history of MI or coronary revascularization procedure were excluded from the cohort. The primary outcome was the composite of nonfatal MI, coronary artery bypass graft, and coronary angiography. After a mean follow-up of 3.3 years, the incidence rates for the primary outcome were 19.8 and 10.3/1000 person-years in the AKI and non-AKI groups, respectively. AKI was associated with a higher risk of coronary events (HR 1.67, 95% CI 1.36–2.04) independent of progression to CKD and ESRD. Notably, the increased risk of coronary events in AKI survivors was similar to patients with diabetes, a well established and potent risk factor for cardiac morbidity.

In a separate study using similar methodology, the same group found an increased risk of stroke after dialysis-requiring AKI [33▪]. The incidence rates for stroke were 15.6 and 11.5/1000 person-years in the AKI recovery and non-AKI groups, respectively (adjusted HR 1.25, 95% CI 1.10–1.65).

The biological link between AKI and cardiovascular disease is not clearly defined but there are several plausible explanations. The frequency with which CKD develops or is exacerbated after an episode of AKI may mediate this relationship given the well described impact of CKD on cardiovascular disease [34,35].The role of post-AKI hypertension as a potential mediator of cardiovascular risk was recently highlighted by Hsu *et al.* [36▪▪] in a retrospective cohort study of 2451 previously normotensive patients who survived an AKI hospitalization. Survivors of AKI were more likely than those without AKI to develop hypertension over a 2-year follow-up period (46.1 vs. 41.2%), with the difference becoming evident within 180 days. In a multivariable model, AKI was independently associated with developing elevated blood pressure during follow-up [odds ratio (OR) 1.22, 95% CI 1.12–1.33].

OTHER LONG-TERM RISKS AFTER AN ACUTE KIDNEY INJURY HOSPITALIZATION

A series of studies from the National Taiwan University Study Group on Acute Renal Failure have provided further insights into nonrenal noncardiovascular outcomes after an AKI episode. The group demonstrated links between AKI and subsequent severe sepsis [37], tuberculosis reactivation [38], malignancy [39], and fractures [40]. Though it remains unclear whether these clinical events are causally mediated by the preceding episode of AKI, these findings serve as a further reminder that AKI survivors constitute a 'high-risk' population.

OUTPATIENT FOLLOW-UP OF ACUTE KIDNEY INJURY SURVIVORS

Though their risk of CKD and other adverse events is high, specialized nephrology care following an episode of AKI has been sparse at best. The US Renal Data System reported that only 13% of patients with hospital-associated AKI saw a nephrologist within 3 months of hospital discharge [41]. A multicenter retrospective cohort of AKI survivors from the US Veterans Administration database used a competing risk approach to determine patient outcomes, with 1-year follow-up commencing 30 days after the peak serum creatinine associated with the AKI episode. Among the 3929 patients whose eGFR remained below 60 ml/min/1.73 m^2, 44% recovered kidney function, 12% died, and 9% were referred to a nephrologist. Referral rates did not vary by AKI severity or levels of eGFR at hospital discharge [42]. Other studies have shown that among patients who survive an episode of dialysis-requiring AKI, reflecting the patient subset with the most severe AKI, only a minority see a nephrologist in the months following hospital discharge [43■■,44■■].

Hospital readmissions may also shed light on the postdischarge care of AKI survivors. Koulouridis *et al.* [45■■] examined readmission rates in 3345 AKI survivors. Compared with non-AKI patients, the AKI group had a significantly higher 30-day hospital readmission risk (11 vs. 15%, OR = 1.21). Limitations of this study include the single-center design and the predominance of stage 1 AKI [45■■]. Horkan *et al.* [46■■] studied readmission rates in a cohort of critically ill patients with AKI. The absolute risk of 30-day readmission was 12.3, 19.0, 21.2, and 21.1% in patients with no AKI, risk ($\geq$50% creatinine increase), injury ($\geq$100% creatinine increase), or failure ($\geq$200% creatinine increase), respectively [46■■]. Brown *et al.* [47] found a similar readmission trend among cardiac surgery patients who experienced AKI, with 30-day readmission rates of 9.3, 16.1, 21.8, and 28.6% in patients without AKI, and stages 1, 2, and 3 AKI (using the Acute Kidney Injury Network classification), respectively. Patients with full recovery of AKI prior to discharge still had high rates of readmission compared with patients without AKI (21 vs. 10%).

The mechanism for the excess readmission rates in AKI survivors was not elucidated in these studies. Understanding the precipitants for these readmissions and their preventability is crucial to shaping effective postdischarge strategies for this population.

A ROLE FOR AN ACUTE KIDNEY INJURY FOLLOW-UP CLINIC

Although the care elements driving improved outcomes with nephrologist-based care are not fully understood, likely contributors include better recognition and control of CKD complications and attention to cardiovascular risk factors [48]. An analogous rationale for nephrologist-led follow-up might also apply to patients who survived AKI, who are also at increased risk for both kidney and cardiovascular events. Unlike specialized CKD care, which is widely established, there are few existing outpatient care models dedicated to patients who survive an episode of AKI.

Brito *et al.* [49] followed 212 patients with presumed acute tubular necrosis for a median of 24 months. Follow-up visits occurred every 3 months during the first year, every 6 months in the second year, and then annually thereafter. Patients with a baseline eGFR < 30 ml/min/1.73 m^2 were excluded. Risk factors associated with long-term mortality included older age (HR 6.4, 95% CI 1.2–34.5) and higher serum creatinine after 12 months of follow-up (HR 2.1, 95% CI 1.14–4.1 per 9 μmol/l). Macedo *et al.* [50] followed 84 AKI survivors for a median of 4.1 years. Patients were seen 1–2 weeks after discharge and quarterly thereafter until serum creatinine stabilized. Each patient's kidney function had stabilized by 18 months. Risk factors associated with kidney nonrecovery were age (OR 1.09, 95% CI 1.04–1.15/year) and serum creatinine at hospital discharge (OR 2.48, 95% CI 1.28–4.73 per 88 μmol/l).

A visit with a nephrologist within 90 days of hospital discharge has been associated with enhanced survival during the post-AKI period [43■■]. Harel *et al.* used Ontario-wide administrative databases to identify survivors of dialysis-requiring AKI who survived to 90 days following discharge. All-cause mortality was lower in patients with nephrology follow-up compared with propensity score-matched AKI patients without such follow-up (HR 0.76, 95% CI 0.62–0.93). Table 2 lists patient characteristics that, in our opinion, should prioritize a patient who experienced AKI for specialized follow-up care.

At our center, we have recently established an ambulatory care program devoted to AKI survivors [51■]. Patients who survive a hospitalization that was complicated by severe AKI (Kidney Disease: Improving Global Outcomes stage 2 or above) are booked into our AKI follow-up clinic within 30 days

Table 2. Characteristics of patients who should be prioritized for early outpatient follow-up with a nephrologist after an episode of hospital-acquired acute kidney injury

Baseline chronic kidney disease
Diabetes mellitus
Heart failure
Receipt of dialysis for AKI
Serum creatinine greater than 25% of pre-AKI baseline at hospital discharge

AKI, acute kidney injury.

of discharge for an initial visit; this is followed by visits at 2–6 month intervals lasting until 1 year after the initial clinic visit. A nephrologist assesses patients at every visit. Clinic visits consist of a standardized assessment that highlights blood pressure and urine albumin control, review of core laboratory studies that are obtained quarterly (hemoglobin, electrolytes, serum creatinine, calcium, phosphate, and urine albumin to creatinine ratio), cardiovascular risk modification, management of CKD complications, medication reconciliation, and specialist referrals for comorbidity management. After 1 year of follow-up, prespecified 'graduation' criteria are used to discharge patients to their family physician or to refer for further nephrology care. We are currently evaluating our AKI follow-up program in a multicenter randomized trial comparing referral to clinic vs. usual care to determine if specialized post-AKI care will improve outcomes (ClinicalTrials.gov NCT 02483039).

CONCLUSION

Although the causal nature of the relationship between AKI and downstream adverse events remains a topic of debate [52,53], there is no doubt that an episode of AKI is a beacon for subsequent adverse health outcomes. Sadly, there appears to be a profound under-recognition of the postdischarge implications of AKI. Further research is needed to develop risk prediction models for adverse outcomes after AKI, determine treatment targets, and evaluate the effect of interventions such as early nephrologist follow-up. Until such time, healthcare providers should be aware that AKI has ramifications that extend beyond hospital discharge and should consider instituting practices to ensure that AKI patients receive outpatient care that is commensurate with their high-risk status.

Acknowledgements

None.

Financial support and sponsorship

S.S. is supported by a Kidney Research Scientist Core Education and National Training Program Post-Doctoral Fellowship (cofunded by the Kidney Foundation of Canada, Canadian Society of Nephrology, and Canadian Institutes of Health Research). This work was supported by the St. Michael's Hospital Academic Health Sciences Centre Alternate Funding Plan Innovation Fund.

Conflicts of interest

There are no conflicts of interest.

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