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**Short- and long-term survival after acute kidney injury**

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**Introduction**

Acute kidney injury (AKI) is a heterogeneous syndrome encompassing a broad spectrum of insults and changes in function that occur acutely to the kidneys [1]. This syndrome is increasingly encountered in sick hospitalized patients, in particular those admitted to intensive care [2–4]. This recent increase in the occurrence of AKI probably reflects not only changes in the characteristics of hospitalized patients (i.e. aging population, greater burden comorbid disease, severity of illness) but also perhaps a corollary of achievements made by modern medicine (i.e. more complex interventions, capability of advanced and prolonged life support) [5].

The development of AKI undoubtedly has important implications on both short- and long-term morbidity and mortality [6]. Observational data consistently indicate that 4–5% of all critically ill patients develop severe AKI and require initiation of renal replacement therapy (RRT) [7–9]. This cohort generally has a poor prognosis with mortality rates often exceeding 60% [7–9]. Moreover, survivors often have protracted stays in ICU and hospital, mild declines in health-related quality of life, impairments in functional status and their care consumes enormous health resources [8,10–12]. Despite this, the available literature provides surprisingly little insight into the long-term kidney prognosis for these patients.

The risk of developing AKI associated with critical illness is likely modified by the presence of pre-morbid chronic kidney disease (CKD) [13]. Similarly, the development of AKI in those with CKD may modify the natural history of their illness and accelerate progression towards end-stage kidney disease (ESKD) and dialysis dependence [14]. Overall, an estimated 8–22% of critically ill patients suffering an episode of severe AKI fail to recover kidney function during hospitalization and need to be discharged on chronic dialysis [8,9,15]. Yet, there is a paucity of data exploring the impact of only partial or incomplete recovery of function in those surviving critical illness.

In the last few years, a consensus definition and classification scheme for AKI, the RIFLE criteria, has been developed, validated and shown to have predictive ability, robustness and clinical relevance across a range of settings [16–20]. This has been a key advance for both clinical care and research activities in a field that was previously beleaguered by the lack of a standardized definition [21]. The RIFLE criteria also share some commonality with the recently developed staging criteria for CKD proposed by the Kidney Disease Outcomes Quality Initiative (K/DOQI) [22]. While the RIFLE criteria incorporate two outcome stages associated with AKI (i.e. loss, ESKD), these are likely insufficient over the long term for those patients with incomplete...
recovery and persistent dysfunction yet not requiring dialysis. Accordingly, the RIFLE and K/DOKI criteria likely have important complementary roles for describing the short- and long-term clinical consequences of AKI.

Thankfully, there is renewed interest in describing the epidemiology and short- and long-term clinical outcomes associated with AKI, as defined by the RIFLE criteria, across a variety of clinical contexts. Until now, however, no studies have evaluated the short-term survival of stroke patients whose course in hospital was complicated by the development of AKI [23] nor the long-term survival and kidney prognosis of patients developing severe AKI requiring RRT associated with an admission to intensive care [24].

Stroke is a leading cause of death and disability [25]. Several factors, including older age, burden of comorbid disease and type of stroke (i.e. ischaemic, haemorrhagic), have been shown to modify the short-term prognosis in acute stroke [25]. Likewise, the presence of CKD has been found to be both a risk factor for stroke and a determinant for reduced long-term survival [26,27]. However, there is a scarcity of literature exploring the impact of development and severity of AKI on stroke prognosis. Accordingly, the study by Covic et al. is indeed welcome. These authors have performed a retrospective 1-year population-based evaluation of consecutive patients hospitalized for first ever CT-confirmed stroke from a single academic centre servicing a defined geographic population [23]. Of 1090 patients with stroke, 14.5% developed AKI, defined by the RIFLE criteria, during hospitalization. Of these, 73% fulfilled the risk, 21% the injury and 6% the failure categories, respectively. The proportion receiving RRT was not reported. Those developing AKI were older, with greater comorbid disease (i.e. diabetes mellitus, ischaemic heart disease, congestive heart failure) and had higher baseline serum creatinine values. Unfortunately, however, the authors did not report the prevalence of CKD in their cohort. The key finding from this study was the 3.4-fold increased crude risk of 30-day mortality for those stroke patients whose course was complicated by AKI (43.1% for AKI versus 12.8% for no AKI, \( P < 0.001 \)) with the majority of deaths occurring early (i.e. within 14 days). Moreover, crude mortality was significantly correlated with increasing severity of AKI (30.4% for risk, 72.7% for injury, 90% for failure, \( P < 0.001 \)). While the most significant predictor of death by multivariable analysis was the type of stroke, the impact of AKI was evident.

There are some potential limitations to these data. Specifically, the RIFLE criteria used in this study omitted the urine output criteria, baseline serum creatinine was assumed as the value at admission to hospital and the authors did not account for in-hospital stroke patients or the impact of severe stroke prompting mechanical ventilation and admission to intensive care. In addition, the observed rate of AKI may have been confounded by all patients having received contrast-enhanced imaging that may have predisposed to contrast-induced nephropathy.

Finally, no data were provided on the timing of occurrence of AKI (i.e. early versus late) in the course of illness, a factor previously shown to modify survival [28]. Nonetheless, the authors have clearly shown the negative association on short-term survival of both the presence and severity of AKI complicating acute stroke.

The recovery of kidney function following AKI is an important determinant of morbidity and may have long-term implications for the health and well-being of patients; however, there has been a dearth of investigations on this topic [29]. Accordingly, the long-term follow-up study by Schiffl and Fischer is an important addition to our understanding of the natural history of AKI in critical illness. These authors performed a prospective 5-year follow-up study of 425 patients with severe AKI treated with RRT [24]. Notably, no patient had evidence of pre-existing CKD when defined by radiologic signs of CKD, persistent abnormal urinalysis or a decreased estimated glomerular filtration rate (eGFR) or elevated serum creatinine (>1.3 mg/dL (115 \( \mu \)mol/L)). The RIFLE and K/DOKI CKD criteria were used to define and describe AKI and long-term recovery and changes to kidney function, respectively.

There are several interesting findings in this study. First, the results clearly confirm the poor survival of critically ill patients with AKI [30]. Moreover, the risk of death appeared to extend well beyond hospital discharge with significant declines in the survival curve not stabilizing until after 1 year. This long-term risk of death was significantly higher for those with a higher burden of comorbid disease, surgical disease and, most importantly, those not achieving complete recovery of kidney function (hazard ratio 4.14, \( P < 0.001 \)). At the time of hospital discharge, only 57% had achieved complete recovery, defined as an eGFR within 10% of baseline, while the remaining 43% had partial recovery and no patient was receiving chronic dialysis. This is the first investigation to clearly show how partial recovery of kidney function after an episode of AKI significantly modifies long-term survival. Such partial recovery would fulfill the definition for stage 2–4 CKD. These findings are rather analogous to studies on the long-term survival of critically ill septic patients, where an increased risk of death persists for several months to years beyond the index hospitalization [31,32].

Second, after the 1-year follow-up, only 27% of those with partial recovery had meaningful improvements in their eGFR with 8.2% fully recovering. On the other hand, 10% had further declines in function. Thus, at 1 year, 26% of survivors had evidence of CKD (stages 2–5). At 5 years, the prevalence of CKD in survivors was only 14%, yet, the apparent improvement in time was largely attributable to deaths for those who had partial recovery. This study has also shown that if patients failed to normalize function by 6–12 months after their episode of AKI, no further recovery occurred. Remarkably, only 2% of survivors progressed to ESKD and required re-initiation of dialysis. However, this rate may be biased by the re-initiation of RRT not being offered or willingly considered by all patients and/or patient death.

Third, critically ill patients with more than one discrete kidney insult (i.e. due to sepsis, shock, nephrotoxins, surgery) while developing or during recovery from AKI were significantly less likely to completely recover function (76% for one insult versus 30% for ≥ two insults, \( P < 0.001 \)). While this finding may seem intuitive to most, it certainly warrants closer examination. Critically ill
patients are commonly exposed to a host of potential kidney insults during their illness, some modifiable and some not. The interaction between repeated insults and new injury to the kidneys is well recognized, but until now, the impact on long-term recovery of function has been poorly characterized. In a multi-centre French study, Guerin et al. found that more than one episode of AKI [defined by serum creatinine > 3.4 mg/dL (300 µmol/L), urine output < 500 mL/24 h or requirement for RRT] independently predicted lower survival; however, no data were available on recovery [28].

There are some notable limitations to these data. In particular, the study was conducted over 15 years and largely reflects the experience of a single academic institution. Yet, Schiff and Fischer have expanded our understanding of the long-term survival and kidney recovery of critically ill patients with severe AKI.

While these two investigations have undoubtedly broadened our understanding of the short- and long-term impact of AKI, additional queries naturally arise. Further prospective evaluations of AKI in specific high-risk populations, such as acute stroke, would clearly appear justified. Similarly, additional studies on the long-term outcome of severe AKI in critically ill patients are needed, in particular, to further explore the association of multiple insults on recovery and the natural history of partial recovery.

Conflicts of interest statement. None declared.


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