Nephrol Dial Transplant (2008) 23: 2235–2241
doi: 10.1093/ndt/gfn182
Advance Access publication 11 April 2008

Original Article

NDT
Nephrology Dialysis Transplantation

Five-year outcomes of severe acute kidney injury requiring renal replacement therapy

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Abstract

Background. Current research priorities in critical care medicine are focusing on long-term outcomes of survivors of critical illness. Severe acute kidney injury (AKI) is a common occurrence in intensive care. However, few studies have followed up these patients beyond 12 months after hospital discharge.

Methods. Of a cohort of 425 patients, 226 survivors with severe AKI necessitating renal replacement therapy (RRT) were followed up for 60 months after hospital discharge. None of these patients had pre-existing kidney disease. Vital status and renal function were documented annually for 5 years.

Results. None of the discharged or transferred patients was dependent on RRT; 57% had complete recovery and 43% had partial recovery of renal function. During the first year after hospital discharge, 18% of survivors died, during the second year 4% and during the third to fifth year 2% per year. At 5 years, 25% of the cohort were still alive. Further improvement in renal function (eGFR) was noted in 26 patients within the first year only. Deterioration of renal function occurred in eight patients. At 5 years, renal function was normal in 86% of the remaining survivors, it was impaired in 9% and 5% of the patients alive needed dialysis again. The proportional Cox regression analysis model showed that pre-existing extrarenal comorbidity, surgery and partial recovery of renal function were independent determinants of long-term survival.

Conclusions. This prospective observational study indicates that severe AKI is not only a determinant of excess in-hospital case fatalities of critically ill patients, but it also carries significant implications for long-term mortality.

Keywords: acute tubular necrosis; acute kidney injury; critical illness; long-term outcome

Introduction

The recovery of renal function after an episode of severe acute kidney injury (AKI), particularly in critically ill patients, is increasingly identified as an important clinical outcome measure of this renal syndrome [1]. Failure to recover complete renal function can have a negative impact on the individual patient's health status. As recognition of the importance of chronic kidney disease as a major cardiovascular risk factor gains momentum, it will become even more important to follow-up those patients who survive AKI but have residual or progressive renal dysfunction [2]. Moreover, the need for regular renal replacement therapy places patients with lost renal function at a high risk for death and impairs severely the quality of life of these patients. Finally, AKI may be an underestimated link between chronic kidney disease and end-stage renal disease (ESRD). The estimated incidence of ESRD from AKI survivors is 4.9 per 100 000 in the USA. This implies that non-recovery from AKI is a major cause of ESRD, similar in importance to diabetes mellitus or hypertension and ahead of glomerular disease and cystic kidney disease [3]. The provision of outpatient RRT for these patients is associated with considerable healthcare costs.

Traditionally, most studies of severe AKI in the critically ill patients have focused on short-term outcomes often associated with hospital discharge. There is paucity of studies describing the long-term outcome and degree of residual renal impairment in the surviving patients. These few studies reporting renal recovery have fundamental but important disparities in the study design (prospective versus retrospective), cause and severity of AKI (all causes versus ATN, conservative treatment and renal replacement therapy versus RRT), number and characteristics of the study population (<100 patients, renal ward and intensive care unit patients), or timing and completeness for ascertainment of long-term prognosis [4–5].

The aims of the present prospective observational study were (a) to provide a more complete picture of patient prognosis and renal recovery and (b) to test the hypothesis that chronic kidney dysfunction secondary to AKI influences patient morbidity and mortality in a well-defined cohort of critically ill patients with severe AKI requiring RRT.

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Subjects and methods

Study design

This prospective 5-year follow-up observational study was carried out according to the principles of the Declaration of Helsinki. The nature of the study was explained in detail to the patients or their next of kin. They all consented to participate in the investigations. The Ethics Committee approved the study protocol.

Study cohort

Selection criteria, renal characteristics of patients and renal replacement therapy have been previously described in detail [6]. Briefly, 425 consecutive critically ill patients with severe AKI receiving RRT at the dialysis unit of the Medizinische Klinik-Innenstadt (October 1990–October 2001) formed the cohort. None of the patients had radiological signs of chronic kidney disease, persistent abnormal urinalysis or decreased estimated glomerular filtration rate (eGFR) or raised serum creatinine levels (1.3 mg/dl).

The patients underwent RRT for one or more of the following indications: volume overload with pulmonary oedema inadequately controlled by diuretics, hyperkalaemia refractory to conservative measures, need for hyperalimentation in the presence of oliguria, uraemic signs or symptoms and/or a blood urea nitrogen concentration >100 mg/dl. RRT consisted of conventional intermittent haemodialysis or continuous techniques. RRT was terminated when blood urea nitrogen or serum creatinine fell spontaneously and/or urine output increased significantly.

Outcome parameters

The primary outcome measures of the study were survival and renal function of the patient cohort at hospital discharge, at 1, 2, 3, 4 and 5 years after hospital discharge. The follow-up period ended for all patients in October 2006. Information related to long-term outcome was obtained either from patients, their relatives or their family doctors.

Definition and classification of AKI

The severity of AKI at initiation of RRT was defined by the first three categories of the RIFLE classification scheme (risk, injury and failure). The RIFLE class was determined based on the worst of glomerular filtration rate criteria (increase of serum creatinine above the baseline serum creatinine level or decrease in estimated glomerular filtration rate) or urine output criteria.

Definition of renal recovery

Recovery of renal function at hospital discharge or transfer of the patient to another hospital was classified as complete, partial or absent.

Complete renal recovery was defined as the return of decreased kidney function to pre-AKI baseline levels of calculated glomerular filtration rate (±10%). Recovery of renal function was defined as partial if a persistent change of glomerular filtration rate from baseline remained evident, but not including the continued requirement of the patient for RRT. The need for RRT at discharge was defined as dependence on life-sustaining RRT both for persistent AKI and for progression to ESRD after 3 months. Persistent AKI was defined as need for RRT for >4 weeks (complete loss of kidney function, RIFLE Class L), whereas end-stage renal failure was defined by the need for dialysis for >3 months (RIFLE Class E). The recurrent need for RRT was defined as initial recovery to independence from RRT, but with subsequent progression of residual chronic kidney disease to ESRD requiring reinstitution of RRT.

Renal function during follow-up

The glomerular filtration rate (eGFR) during the follow-up was estimated from serum creatinine using the simplified MDRD (modification of diet in renal disease) equation based on age, gender, race and calibration for serum creatinine. Normal renal function was defined as an eGFR >90 ml/min/1.73 m^2. Individuals with decreased levels of GFR were classified according to the stages of chronic renal disease.

Clinical data recorded during hospital stay

The following variables were recorded at initiation of RRT: age, gender, extrarenal comorbidity by the Charlson comorbidity index [7], cause of AKI, renal laboratory data, urine output, mode of RRT and severity of illness by the APACHE II score.

Statistical analysis

Continuous variables were reported as mean ± SD and compared among subgroups using the nonparametric Wilcoxon–Mann–Whitney test.

Categorical data were expressed as proportions and compared among subgroups using Fisher's exact test. Multivariate survival analysis was performed by the Cox model. The log-likelihood ratio test was used for model comparison and goodness-of-fit assessment. The final most parsimonious model was obtained by backward selection from the maximal model composed of the variables: age, gender, type of admission (surgical, medical), AKI etiology (septic, non-septic), pre-existing extrarenal comorbidity (presence, absence) and level of recovery of renal function (normal renal function, partial recovery). Survival curves were estimated by the Kaplan–Meier method and differences between curves were analysed with the log-rank test.

A two-sided *P*-value of 0.05 was considered significant. All statistical analyses were performed with SPSS version 10 (SPSS Inc., Chicago, IL, USA).

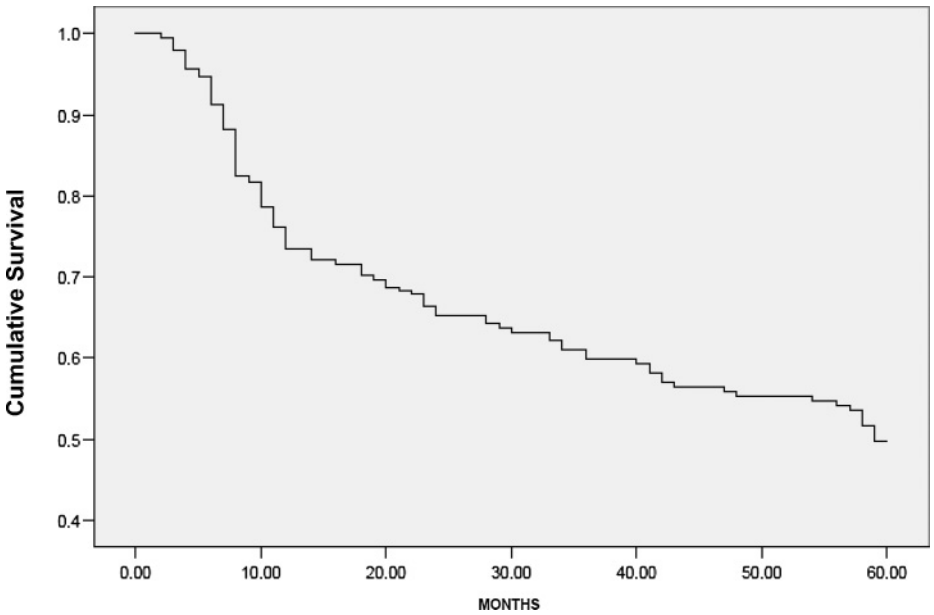

Fig. 1. Kaplan–Meier survival curve of patients discharged alive after severe acute kidney injury necessitating renal replacement therapy.

Results

Baseline demographic data of the cohort at the start of dialysis

During the study period, 425 critically ill patients developed severe AKI secondary to ATN with need for RRT. The mean age of the cohort was 65 years; they were predominantly male and had a high burden of comorbid conditions. Normal eGFR prior to the renal insult was documented in each patient. The major cause of AKI was ischaemia (60% of the patients), followed by sepsis in 33% and nephrotoxins in 7% of the patients. The initial mean APACHE III score was 88 (±29). Severity grading of AKI according to the RIFLE criteria at the start of RRT revealed RIFLE class F for all the participating patients. RRT encompassed intermittent haemodialysis in 68% of the patients, CRRT (continuous veno-venous haemodialysis or continuous veno-venous haemodiafiltration) in 13% and a combination of IHD and CRRT in 19%.

In-hospital outcome of cohort

The overall in-hospital mortality of the 425 critically ill patients with severe AKI secondary to ATN was 47%. At hospital discharge, recovery of renal function was complete in 57% surviving patients as assessed by eGFR. Forty-three percent had partial recovery of renal function (eGFR < 90 ml/min/l.73 m^2). None of the surviving patients had continued need for RRT at discharge. Of interest, 97 of the 226 surviving patients had at least two major renal insults precipitating and aggravating AKI. Amongst them ischaemia and re-operation, sepsis and surgical procedure, nephrotoxic agent and sepsis or nephrotoxic agent and hypotension or sepsis and nephrotoxic drugs occurred either during development of AKI or during dialysis dependence within the same AKI episode. These insults occurred either concurrently or separately within days. Only 27 patients of this subset of ATN patients regained normal renal function compared with 99 out of 129 patients with presumed one major renal insult ($P < 0.001$).

Five-year follow-up of outcome of patients surviving an episode of ATN RRT

Only one patient was lost definitively for follow-up, and up to three patients were missed temporarily. During the first year after hospital discharge, 76 patients (18% of total cohort) died. During the second year, 4% of the cohort died. The mortality rate in Years 3–5 was 2% of the cohort per year. One hundred and twenty patients died during the follow-up period of 5 years, i.e. 47% of the survivors or 25% of the total cohort were alive at 5 years (Figure 1).

None of the patients discharged with complete recovery function showed any deterioration of renal function during the 5 years of observation.

During the first year of follow-up, 26 patients showed an improvement of eGFR, and eGFR normalized in 10 of these patients. Eight patients with chronic renal insufficiency demonstrated a progressive decrease in eGFR without evidence of any acute kidney injury.

Renal function in patients surviving after 5 years was normal in 86%; eGFR was impaired in 9% and 5% of the survivors at that time needed maintenance dialysis. Thus, 2% of all survivors needed RRT again. ESRD secondary to severe AKI occurred in 1% of the patients of the total cohort (Table 1).

Analysis of factors associated with long-term mortality among critically ill patients with severe AKI

Long-term survivors from severe AKI were significantly younger, had significantly lower extrarenal comorbidity,

Table 1. Long-term renal outcomes in survivors of severe AKI necessitating RRT

Renal function	At 1 year	At 2 years	At 3 years	At 4 years	At 5 years
Number of patients	150	133	123	115	106
Normal eGFR (90+)	111 (74%)	101 (76%)	98 (79%)	94 (82%)	91 (86%)
CKD					
Stage 2 eGFR 60–90	16 (11%)	10 (8%)	8 (7%)	7 (6%)	3 (3%)
Stage 3 eGFR 30–59	17 (11%)	13 (10%)	8 (7%)	5 (4%)	3 (3%)
Stage 4 eGFR 15–29	5 (3%)	7 (5%)	5 (4%)	5 (4%)	4 (4%)
Stage 5 dialysis	1 (1%)	2 (1%)	4 (3%)	4 (3%)	3 (3%)

Numbers are given as absolute numbers and percentage (parenthesis).
eGFR: estimated glomerular filtration rate (ml/min/1.73 m^2); CKD: chronic kidney disease.

Table 2. Demographic factors associated with long-term mortality of survivors of severe AKI necessitating RRT

	Dead	Alive	*P*-value
Number of patients	120	106	
Age (years)	68 (10)	58 (12)	0.001
Gender (M/F)	78/42	60/46	NS
Admission surgery/medicine	54/66	20/86	0.001
Comorbidity index	1.7 (1.1)	0.7 (0.4)	0.001
Cause of AKI septic/non-septic	47/73	37/69	NS
RRT IHD/CRRT	60/60	64/42	NS
Renal functional recovery partial/complete	75/45	15/91	0.001

Data are given as mean ± SD (parentheses) or as absolute numbers.
AKI: acute renal injury; RRT: renal replacement therapy; IHD: intermittent haemodialysis; CRRT: continuous renal replacement therapy; NS: not statistically significant.

Table 3. Cox proportional hazards regression showing the effects of various variables on the risk of death of long-term survivors of severe AKI

Variable	*B*	SE	RR	Lower 95% CI	Upper 95% CI	*P*-value
Comorbidity	1.046	0.226	2.845	1.829	4.427	0.001
Surgery	0.487	0.186	1.628	1.131	2.342	0.009
Chronic kidney disease	1.421	0.196	4.141	2.819	6.082	0.001

Log likelihood ratio 1127.0.

underwent less surgical procedures and regained significantly more often complete recovery of renal function than patients dying during the follow-up study (Table 2).

Multivariate analysis performed by the Cox model showed that the independent variables predicting long-term survival were the presence of pre-existing comorbid factors, surgical admission and partial recovery from acute renal failure (Table 3).

Kaplan–Meier survival curves (Figures 2–4) showed that patients with no extrarenal comorbidity had a significantly better survival than patients with extrarenal comorbidity. Furthermore patients with post-surgical AKI had worse survival than medical patients. Patients with complete renal recovery after severe AKI had better survival than patients with chronic renal failure secondary to severe AKI.

Discussion

The main results of this long-term follow-up of a cohort of critically ill patients with severe AKI document that the assessment of outcomes at ICU or hospital discharge underestimates morbidity and mortality of severe AKI. The prospectively defined outcomes of this study, namely a case fatality rate of 75% in 5 years and a renal recovery rate of 86% in 5-year survivors, highlight the fact that surviving patients of AKI requiring RRT remain ill for years.

Specific data on long-term outcomes for severe AKI are limited, and there are substantial differences among the few published studies. The present observational study of a cohort of critically ill patients with severe AKI requiring RRT was prospectively conducted and limited to patients with normal renal function prior to the renal insult. Only one patient was lost during the 5-year follow-up period. The characteristics of the cohort such as high mean age, predominance of male patients, burden of comorbid disease and the presumed main causes of AKI, all reflect the changing spectrum of patients with AKI in a current mixed (surgical, medical) ICU. Liano *et al*. [5] published the long-term outcome of 187 patients surviving ATN. None of these patients had previous nephropathy. A comparison of the two studies, however, is hampered by the fact that 70% of the Madrid patients had ATN not requiring RRT and that 57% of the patients were not treated in the ICU [5].

A high proportion of critically ill patients with AKI requiring RRT died before discharge from the hospital. The

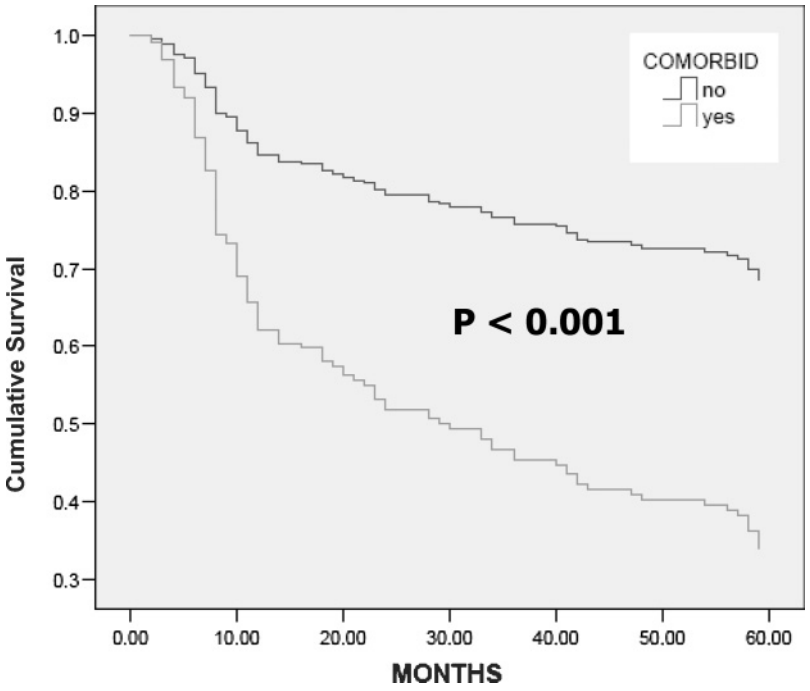

Fig. 2. Kaplan–Meier survival curve of patients with or without pre-existing extrarenal comorbidity.

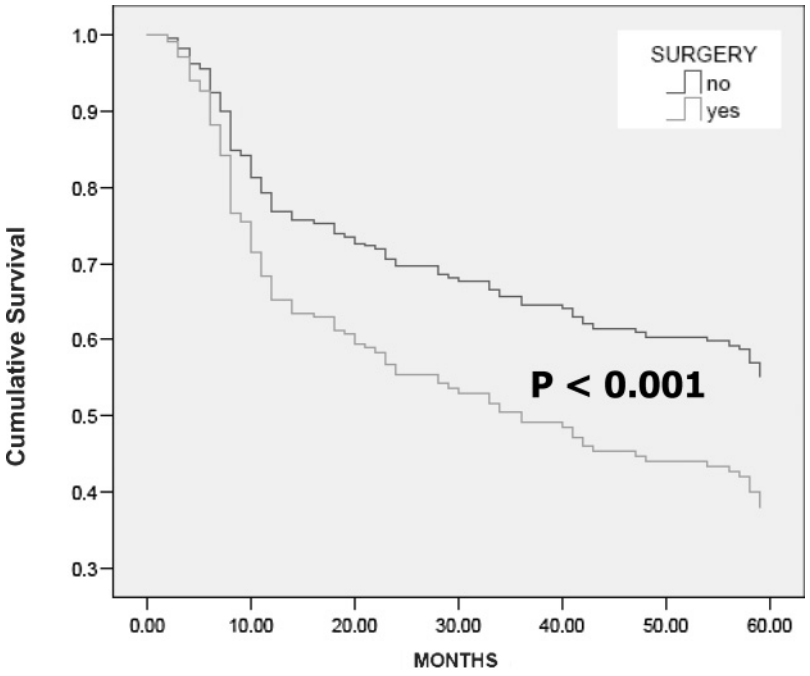

Fig. 3. Kaplan–Meier survival curve of surgical and medical patients.

overall in-hospital mortality of this cohort was 47% and is in agreement with data from a recently published systematic review of other studies [8]. In the present study the 1-year mortality rate was 65%, the 2-year mortality rate was 69% and the 5-year mortality rate was 75%. Ahlström *et al*. [9] analysed 703 patients receiving RRT for (all causes) AKI, either in the ICU or general hospital ward. The median follow-up of these patients was 3.9 years, and the estimated mortality rate at 5 years was 70%. Morgera *et al*. [10] found that ICU patients with AKI necessitating continuous RRT discharged from the hospital had a 50% survival probability after 5 years. Frost *et al*. studied 419 medical and surgical patients with AKI (82% ATN) requiring RRT and found at 5 years a survival rate of 52% for medical AKI and 28% for surgical AKI [11]. Liano *et al*. [5] calculated Kaplan–Meier survival curves showing that 69% of the ATN patients

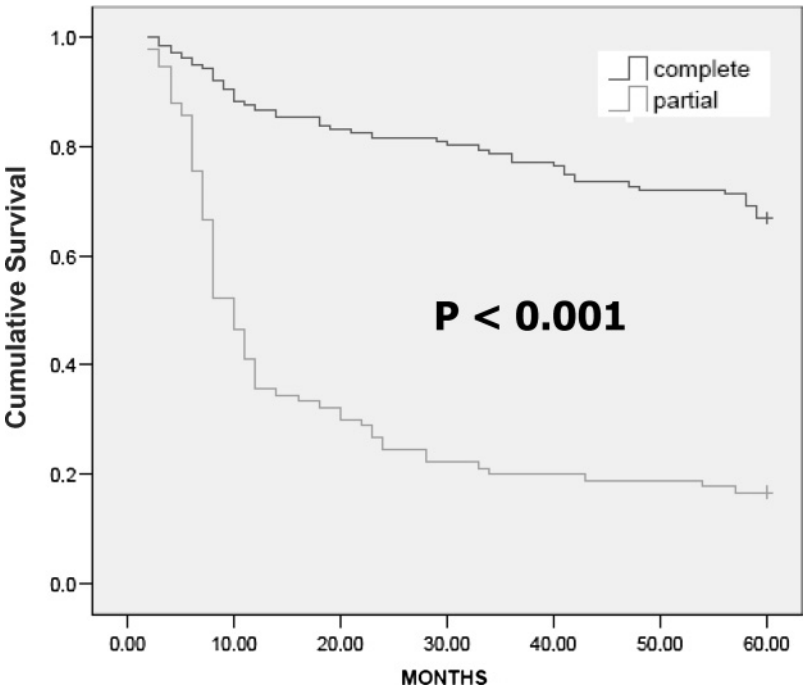

Fig. 4. Kaplan–Meier survival curve of patients with complete or partial renal recovery.

discharged from the hospital were alive at 5 years. The better survival probability of the Madrid patients may, however, be explained by the predominance of mild and moderate ATN cases and less severity of the underlying disease [5].

Comparisons of the long-term survival of ICU patients with severe AKI have typically been compared to the general population. In fact, two adequately powered studies showed higher mortality of AKI survivors after hospital discharge than the control groups [5,11). This difference is well explained by the fact that patients admitted to an ICU have more pre-existing disease before their acute event than the general population.

The analysis of survival rates observed in the present study suggested a three-phase pattern of deaths after critical illness. In phase 1, during the hospital stay, severe AKI requiring RRT had a high case-fatality rate directly attributable to critical illness, pre-existing comorbidity and the acute kidney dysfunction itself. In phase 2, the causes of death of patients are a mixture of underlying diseases as demonstrated by autopsies in the Madrid study [5] and the burden of extrarenal and renal comorbid conditions. The presence of comorbid disease in the present cohort as well as in the Madrid population was associated with a survival rate worse than that observed in patients without comorbid factors.

None of the patients participating in this observational study died with ESRD, but partial recovery with chronic renal insufficiency represented the most important determinant of long-term survival. The same observation was made in the Madrid study [5]. In phase 3, the excess mortality of survivors of severe AKI vanishes and may equal the mortality of the general population.

The present study demonstrates that renal prognosis of patients surviving severe AKI is generally good, particularly in those with previously normal renal function. Fifty-seven percent of the survivors of the present cohort had normal renal function at hospital discharge, 43% left the hospital with partial recovery and no patient needed RRT at hospital discharge. Other studies of critically ill patients with severe AKI requiring RRT reported that, at hospital discharge, 32 or 33% of the patients were RRT-dependent [12,13].

This large discrepancy may be well explained by differences in the cause of AKI and/or inclusion of patients with pre-existing renal disease/insufficiency. The prevalence of causes of AKI other than ATN in ICU patients has been reported to be up to 22% [14]. The frequency of ESRD in survivors of severe AKI was highest in patients with acute parenchymal disease or atheroembolism and lowest in ATN [15]. Pre-existing chronic kidney disease is a risk factor for the development of AKI requiring RTT. The prevalence of pre-existing renal disease has been estimated to be up to 30–35% [16,17]. Of importance is the observation that these patients with acute on chronic renal failure failed more often to regain adequate renal function than patients with normal renal function prior to AKI [18]. Confirming previous measurements of recovery of glomerular filtration rate by Hall *et al*. [19], we found that, in patients who ultimately experienced complete functional recovery, the maximal rate of return of renal function was attained within 6–12 months. Functional recovery occurred significantly less in patients who had repeated episodes of renal ischaemia and/or nephrotoxin administration during the same episode of acute kidney injury. Whether the mode of RRT may have an impact on the recovery of renal function as suggested by some [20,21] remains to be seen.

The degree of persistent loss of renal function during follow-up was variable. None of the patients of this cohort recovered normal renal function as late as 12 or more months after discharge. In contrast, renal function in a proportion of patients with partial recovery deteriorated further in the course of the observation period. In fact, eight patients with partial recovery suffered from a progression to chronic renal failure; five patients needed to go back on dialysis. These data indicate that severe AKI is not a major contributor to the ESRD population, at least in patients with normal renal function prior to the development of AKI.

At 5 years, 86% of our surviving patients had normal renal function, a finding corroborated by the data of the Madrid study [5].

The interpretation of our study results should bear in mind its limitations. The study was a single-centre study, conducted over 12 years. Patients with pre-existing chronic kidney disease were excluded. The results may be prone to bias due to the observational nature of the study design and we were not able to adjust for all factors potentially contributing to long-term changes to renal functional recovery from acute kidney disease.

Conclusions

Long-term survival after severe AKI is generally poor. Persistent reduction of renal function exhibited important independent effects on outcome that extended well beyond discharge from the hospital. Although renal function normalized in most of the AKI patients without pre-existing chronic kidney disease, the subgroup of patients with chronic renal dysfunction suffered a higher mortality. Severe AKI necessitating RRT should no longer be simply viewed as an acute or short-term illness, but patients should be monitored at least for 12 months.

Conflict of interest statement. None declared.

(See related article by A. Covic *et al*. The impact of acute kidney injury on short-term survival in an Eastern European population with stroke. *Nephrol Dial Transplant* 2008; 23: 2228–2234.)

(See related article by S. M. Bagshaw. Short- and long-term survival after acute kidney injury. *Nephrol Dial Transplant* 2008; 23: 2126–2128.)

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Received for publication: 18.11.07
Accepted in revised form: 7.3.08