Long-term outcomes after acute kidney injury

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Acute kidney dysfunction is a common problem in intensive care units. It is not only associated with increased morbidity and mortality but also with increased healthcare costs. Limited healthcare budgets have now raised the issue of how much therapy should be dedicated to these critically ill patients. A precondition for any further discussion on this topic is the question on the long-term outcome and quality of life of these patients. However, only limited data are available in this field. In this review, we will focus on the existing literature, considering not only acute renal failure patients requiring renal replacement therapy but also those patients with mild or moderate impaired renal function. The intention of this review is to show that acute kidney injury is an important but often underestimated disease and a disease that deserves major attention because it is associated with impaired short- and long-term outcome. We will demonstrate that acute kidney injury patients requiring dialysis have a reasonable long-term survival rate and good quality of life. There is no doubt that aggressive intensive care unit treatment is justified in these patients, irrespective of the health costs. (Crit Care Med 2008; 36[Suppl.]:S193–S197)

Key Words: acute kidney injury; acute renal failure; renal replacement therapy; survival; postdischarge survival; long-term outcome; quality of life

The care of critically ill intensive care unit (ICU) patients is resource intensive, technically involved, and expensive (1). Although only 3–5% of hospital beds are located in the ICU, up to 20–30% of hospital budgets are spent on the ICU (2–4). Acute kidney injury is known to be an independent predictor of poor in-hospital outcome. The higher the degree of renal dysfunction is, the higher the mortality rate (5–7). Acute renal failure (ARF) patients requiring renal replacement therapy are among the most challenging of patients. The condition generally occurs in the course of multiorgan failure and is associated with a poor prognosis (8, 9). Mortality rates are high, ranging between 50% and 80% (10–12). Those patients who need renal replacement therapies frequently require lengthy ICU treatment and extensive life support (13, 14). Recent data (8) suggest that, worldwide, around 6% of patients in the ICU develop ARF, and a significant proportion of these require dialysis (15–17). The mortality of ARF seems to have remained unchanged during the last 30 yrs, despite advances in supportive care (18). This, of course can be clearly attributed to the increasing age and illness severity of these patients. Advanced age, chronic illness, and severity of acute illness have been identified as important prognostic indicators in ARF (16, 19, 20).

Although healthcare providers have not questioned funding for ICU care, limited healthcare budgets have raised the issue of how much therapy should be dedicated to critically ill patients with multiorgan failure and acute kidney injury. Are the extreme expenses justified in regard to the in-hospital mortality rate, the long-term outcome, and the quality of life of these patients? These questions have not yet been fully answered and will probably remain a topic of discussion for years. This review, however, will focus on the long-term postdischarge survival and quality of life in patients with acute kidney injury who were able to leave the hospital. We will try to give an answer to the question of whether our efforts in the ICU are of benefit to our patients.

Long-term Postdischarge Survival

Long-term postdischarge information on critically ill patients surviving ARF is limited. We conducted a study on the long-term outcome of critically ill patients with multiorgan failure, including ARF, requiring renal replacement therapy (21). The University Hospital Charité (Campus Mitte) has a total of 72 ICU beds serving general surgery, cardiac surgery, neurosurgery, orthopedics, neurology, cardiology, general internal medicine, and infectious diseases. It is always an experienced staff nephrologist who determines the need for renal replacement based on clinical grounds. Between 1993 and 1998, 979 ARF patients were treated with continuous renal replacement therapies in our ICU units. The in-hospital mortality rate was 69%. A questionnaire was mailed to all patients who were discharged from the hospital. The questionnaire was designed to address patients' health-related quality of life and to provide information on renal function. In addition, a separate questionnaire was sent to the patients' family doctor or medical specialist, or both, to obtain objective information on renal function, health status, and physical fitness. In case that neither the patient nor the family doctor responded to the questionnaire, the registry office was consulted to find out whether the patient was still alive. By doing so, we were able to obtain postdischarge information from 89% (n = 267) of our patients. The median follow-up time was 938 days (range, 159–2653 days). The overall estimated survival probability (in and out of hospital) was 19% at 1 yr, 16% at 2 yrs, and 14% at 5 yrs. At first view, these data were quite

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discouraging because overall ARF outcome was comparable with malignant diseases like lung cancer (22) and esophageal/gastric cancer (23), with reported 5-yr survival rates of 14% and 18%, respectively. However, the survival probability of those patients who had been discharged from the hospital alive was 77% for the first 6 months postdischarge. Patients surviving 6 months had a probability of 89% to survive the following 6 months. A 50% postdischarge mortality probability was reached approximately 5 yrs after hospital discharge. Thus, postdischarge survival was surprisingly good. Our data are in line with the results obtained from other groups. Gopal et al. (24) studied the long-term survival and out-of-hospital quality of life of critically ill patients with combined multiorgan failure and ARF treated with continuous renal replacement therapy. Patients were recruited from two tertiary institutions. From an initial cohort of 250 patients, 85 patients survived to hospital discharge, corresponding to a hospital mortality rate of 66%. Mean postdischarge follow-up time was 2.5 yrs (range, 0.1–5.3 yrs). A postal questionnaire was sent to all survivors. A total of 33 of the 85 patients (38.8%) did not reply to the questionnaire; 35 patients (41.7%) were alive at the time of response and 17 (20%) were deceased. The authors speculated that even assuming that nonresponders had twice the mortality of responders, the overall survival rate from hospital admission to the time of questionnaire response was approximately 20%, which is in line with our data. In a Finish study, Ahlström et al. (25) analyzed the long-term outcome of 703 ARF patients requiring renal replacement therapy. The median follow-up time was 3.9 yrs postdischarge. They found an overall mortality rate of 41% at 28 days, 57% at 1 yr, and 70% at 5 yrs. In a retrospective, single-center study, Korkeila et al. (26) assessed the long-term outcome of ARF patients in terms of 6-month and 5-yr mortality; 62 ARF patients requiring dialysis were included. ICU and in-hospital mortality rates were 34% and 45%, respectively. In contrast to our study, there was only a minor increase in mortality after discharge from the hospital. Overall mortality was 55% at 6 months and 65% at 5 yrs. The relatively low mortality rate is explained by a quite high proportion of patients (11%) with isolated renal failure due to rhabdomyolysis or intoxication. Ten years ago, Jones et al. (27) retrospectively reviewed 408 consecutively admitted ARF patients treated with continuous renal replacement therapy in the multidisciplinary ICU of a large teaching hospital. All patients were ventilated, and 75% of the patients required inotropic support. The ICU, hospital, and 6-month survival rates were 48%, 38%, and 36%, respectively.

In the last few years, it has become clear that not only ARF requiring dialysis an independent risk factor for poor outcome but any kind of kidney dysfunction (4, 28–31). However, limited data are available about the relationship of severity of renal dysfunction and long-term outcome. Bagshaw et al. (32) very recently conducted a population-based assessment of long-term outcome in critically ill patients, stratified by severity of kidney dysfunction. This is a very interesting study because the authors tried to assess the effect of various degrees of renal dysfunction on long-term outcome. Data were obtained from the official databases of the Calgary Health Region and allowed to provide a complete mortality status at 1 yr, including the in-hospital and out-of-hospital mortality rate. The primary end point was the 1-yr mortality rate categorized by the degree of renal dysfunction. Severity of kidney dysfunction was stratified by using the peak serum creatinine level during ICU admission. Kidney dysfunction was stratified as no renal failure (serum creatinine of <150 μmol/L), mild dysfunction (serum creatinine of 150–299 μmol/L), moderate dysfunction (serum creatinine of >300 μmol/L), and severe ARF with need for renal replacement therapy. During the study period of around 3 yrs, 5,693 patients were admitted to the ICU, with 1,190 patients (20%) fulfilling the criteria of renal dysfunction. Any degree of kidney dysfunction in critically ill patients was associated with decreased long-term survival. Crude 1-yr case-fatality rates stratified by severity of kidney dysfunction were 17% for no renal failure, 47% for mild dysfunction (370 of 790 cases), 48% for moderate dysfunction (77 of 160 cases), and 64% for severe ARF (153 of 240 cases). To our surprise, the 1-yr mortality rate of ARF patients requiring dialysis did not differ extensively from the in-hospital mortality rate. For the severe renal failure group, the mortality rate increased moderately from 60% to 64%. This is a striking difference to our own data and the data from Gopal et al. (24) and can only be explained by a difference in study population. An explanation could be that our study and the study by Gopal et al. (24) were conducted in university hospitals, whereas the data from Bagshaw et al. (32) were collected from a variety of different hospitals, thus representing a larger case mix with probably a higher proportion of less severe critically ill patients.

It clearly makes sense to evaluate long-term outcome in regard to the degree of renal dysfunction. In recent years, the Acute Dialysis Quality Initiative has established a new consensus method of defining and stratifying ARF, taking into account not only the creatinine value but also the glomerular filtration rate and the urinary output (33–35). The new ARF stratification is named the *RIFLE* criteria. RIFLE is an acronym comprising risk, injury, failure, loss, and end-stage kidney disease. It allows a standardized categorization of the various levels of acute kidney injury. Whether the RIFLE criteria are able to reflect the phenomenon of increasing mortality with increasing renal dysfunction has been recently studied by Uchino et al. (31) and by Ostermann and Chang (5). Ostermann and Chang (5) analyzed the Riyadh Intensive Care Unit Program database of 41,972 patients admitted to 22 ICUs in the United Kingdom and Germany between 1989 and 1999. Acute kidney injury occurred in 15,019 patients (35.8%). According to the RIFLE classification, 7,207 patients (17.2%) were at risk, 4,613 (11%) had injury, and 3,199 (7.6%) had renal failure. Patients with risk, injury, and failure classifications had hospital mortality rates of 20.9%, 45.6%, and 56.8%, respectively, compared with 8.4% among patients without acute kidney injury. There is no doubt that the RIFLE criteria are a good tool to characterize the risk for in-hospital mortality. The higher the score, the more severe renal failure is, the higher will be the in-hospital mortality rate. Data are in line with the data reported by Uchino et al (31). In a very recent study, it has been shown that even a mild renal dysfunction had serious consequences in the duration of mechanical ventilation, weaning from mechanical ventilation, and in-hospital mortality in critically ill patients (28). But what about the out-of-hospital mortality rate and the long-term outcome of acute kidney injury patients? Abosaif et al. (7) tried to evaluate the sensitivity and specificity of the RIFLE criteria to predict renal and patient outcomes in critically ill acute kidney injury patients. RIFLE

classification was applied to 183 patients with acute kidney injury admitted to the ICU from 2002 to 2003 at the Northern General Hospital, Sheffield, UK. Patients were divided into four groups according to percentage of decrease in glomerular filtration rate from baseline. The risk group included 60 patients, the injury group 56 patients, the failure group 43 patients, and the control group 24 patients. The 1-month mortality rate in the ICU was significantly greater in the failure group compared with all groups, as was the 6-month mortality rate.

It seems obvious that whenever outcome analyses are performed, there is an attempt to detect special risk groups or risk factors in clinical subgroups. This also holds true for long-term outcome analyses in critically ill acute kidney injury patients. In our study (21), we were able to differentiate various clinical groups and subgroups. We found no difference in the long-term out-of-hospital survival probability between internal medicine and surgical patients (Fig. 1). Cardiac surgery patients requiring prolonged ICU treatment are known to be at risk for poor outcome (36–38). However, even these patients did no more poorly once they left the hospital than other groups. Sepsis, an independent risk factor for poor outcome, is known to be associated with a high in-hospital mortality rate (9, 10, 39, 40), which dramatically increases when ARF also occurs (41). In our study population, septic patients had the highest in-hospital mortality rate (75%) but a tendency toward a better long-term out-of-hospital survival probability. This is in line with other studies conducted in this field. Older patients did worse than younger patients, a natural phenomenon also reported by many other groups (25). Last, but not least, the presence of comorbidities (e.g., diabetes) portended a poorer outcome as well. Landoni et al. (42) studied the long-term survival of cardiac surgery patients requiring renal replacement therapy. Out of 7,846 consecutive patients, 126 patients (1.6%) required postoperative renal replacement therapy. The hospital mortality rate of these patients was 67%, compared with only 1.5% in a case-matched control group. After a mean interval of 3.5 yrs after discharge, the authors were able to interview 22 patients, or 52%, of the ARF survivors. They concluded that if these patients survive to hospital discharge, their long-term outcome (and quality of life) is good. A similar work on a subgroup of patients has been done by Luckraz et al (43). They analyzed the long-term outcome of 92 cardiac surgery patients who developed ARF after surgery. They observed 1- and 5-yr survivals of 53% and 52%, respectively. Again, patients who survive to hospital discharge and do fine for the first 12 months postdischarge have a reasonable long-term outcome.

An interesting and still incompletely answered question is the degree of renal dysfunction after discharge. In the current literature, there are sufficient data about the incidence of postdischarge end-stage renal failure, which ranges between 2% and 15% (27, 43, 44). Data on the incidence or prevalence of persisting renal dysfunction not requiring dialysis are limited. In our study population, information on postdischarge renal function was available in 130 patients, corresponding to 84% of all survivors at the time of investigation. Renal insufficiency persisted in 41% of cases, with a mean creatinine value of 190 ± 95 μmol/L (dialysis patients excluded), and 10% of cases required maintenance dialysis.

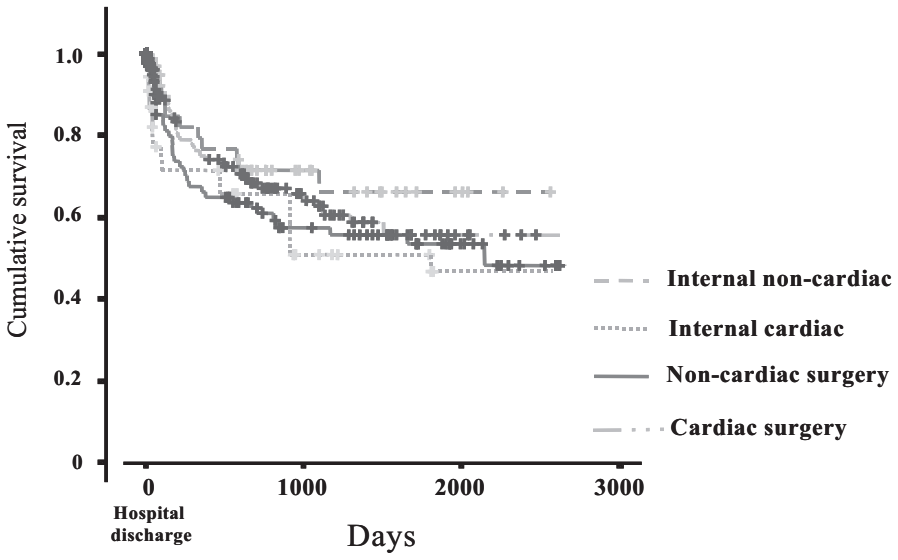

Figure 1. Out-of-hospital survival of acute renal failure patients.

Health-Related Quality of Life

ARF patients surviving their critical illness are often discharged from the hospital in an intermediate state of health. Most of these patients need transient or even permanent help. Whether such patients enjoy a reasonable quality of life has long been unknown, with only limited data available. Studies on quality of life after critical illness usually focus on health-related quality of life (HRQoL), which covers three main aspects, namely, the patient's physical, psychological, and social status (45).

In our retrospective study, the evaluation of HRQoL was a major topic. From the initial cohort of 979 ARF patients, 301 patients survived to hospital discharge. A postal questionnaire was sent to all survivors. The HRQoL questionnaire was designed to evaluate patients' activity, mental function, and health status. The response rate was 53%. We observed a relatively favorable postdischarge quality of life in our patients. Responses to the questionnaire are show in Table 1. Most patients were self-sustaining, physically active, and psychologically balanced. Only a small number of patients felt helpless, depressed, or frustrated.

Studies of the HRQoL of former ARF patients are few. Ahlström et al. (25) evaluated HRQoL in their study population with the EuroQol (EQ-5D) (46) instrument, including a visual analog scale score to evaluate the patient's perceived health. The EQ-5D is a generic, standardized, multidimensional, self-administered instrument designed to measure HRQoL. The EQ-5D includes five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) evaluated on a scale of 1 to 3. The instrument uses a set of population-based preference weights to calculate a single index score representing the overall HRQoL, which facilitates comparison with the age- and sex-matched general population. The EQ-5D instrument also includes a visual

Table 1. Questionnaire sent to acute renal failure survivors for the assessment of health-related quality of life

Since Discharge from the Intensive Care Unit	%
How would you describe your current health?	
Very good; I feel hale and hearty	8.6
Good, only minor limitations	68.1
Bad	20.7
Very bad	2.6
How would you judge your current physical status?	
Normal	7.0
Normal with only minor limitations	38.6
Reduced	32.5
Severely reduced	21.9
How would you describe your mental status? (multiple answers possible)	
Balanced	43.4
Short-tempered	20.4
Fear of worsening of current health	31.9
Depressed	6.2
Frustrated	6.2
Were you able to restart work/your profession?	
Yes	13.3
No	23.0
Not applicable (already retired at the time of hospital admission)	63.7
Do you need outside help in your daily life?	
Self-sustaining	57.4
Temporarily need help (family)	17.4
Need outside help a few hours a day	15.6
Permanent need for help	9.6
How would you judge your current quality of life compared with the time before your hospital stay?	
Significantly improved	13.2
Improved	24.6
Slightly improved	11.4
Unchanged	12.2
Slightly worse	16.7
Significantly worse	21.9

analog scale for self-rating of patients' health, ranging from 0 to 100 (representing the worst and best states imaginable). The median follow-up time was 2.4 yrs for HRQoL. Of the 229 survivors, 153 (67%) responded to the questionnaire. The EQ-5D score was significantly lower in the study population than in the age- and sex-matched general population (0.68 vs. 0.86). The overall quality-adjusted survival was poor (15 quality-adjusted life years per 100 patients in the first year of follow-up). HRQoL remained lower than that of the age- and sex-matched general population. Nevertheless, the perceived health as measured by the visual analog scale score did not differ between the ARF survivors and the age- and sex-matched control group. Median visual analog scale scores were 69.5 and 70.0, respectively. Thus, survivors were as satisfied with their health as the general population. This is in agreement with our study and that of previous studies, too (24, 47). Using the Nottingham Health Profile Score, Gopal et al. (24) found physical pain, interrupted sleep, depression, and loss of mobility and energy to be the most common complaints among their 35 ARF survivors. The follow-up time was 2.5 yrs. However, as in our study, they did not compare the results with the general population. In a very small study of 12 patients, Maynard et al. (47) examined the mental and physical components of the Short Form Health Survey at 6 months after hospital discharge in ARF survivors. Mental and physical health were either comparable or only slightly poorer than that of the general population. In the study of Korkeila et al. (26), the 62 former ARF patients reported good quality of life 6 months after discharge, as measured by the Nottingham Health Profile. Loss of energy and limitation of physical mobility were the most frequently reported complains at 6 months. Functional ability was fairly good at 6 months. Again, HRQoL of the patients was not compared with that of the general population. Landoni et al. (42) found that cardiac surgery patients who experienced ARF and survived to hospital discharge (42 patients) had a reasonable long-term outcome. After a mean observation time of 42 months, 30 out of 42 patients were alive, with only three patients complaining of limitations in daily activities.

CONCLUSIONS

Acute kidney injury is a critical disease with a high in-hospital mortality rate. Not only renal failure requiring dialysis but any kind of renal dysfunction is associated with an impaired long-term outcome. However, those patients who survive to hospital discharge experience a surprisingly good quality of life. Most patients are self-sustaining, physically active, and psychologically balanced. Due to the favorable findings, we consider that aggressive ARF treatments are warranted even in severely ill ARF patients.

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