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Prognosis of acute kidney injury requiring renal replacement therapy in solid organ transplanted patients

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Summary

Solid organ transplanted patients represent a complex and multi-morbid population with potential acute illness. They are at high risk not only for chronic renal failure (CRF), but also for acute kidney injury (AKI) and little is known about the overall epidemiology or prognosis. We conducted a retrospective review of all solid organ transplant patients who required emergency renal replacement therapy (RRT) for AKI during a period of 7.5 years. We identified 53 episodes of AKI requiring RRT occurring in 51 transplanted patients, and 58.5% of them were freshly (<48 h) transplanted when admitted in ICU. The majority of episodes were a result of cardio-circulatory or septic events (84%), and a large proportion of the AKI episodes were a result of multifactorial causes (27%). Overall 90 days mortality was 49%, and no difference was detected between kidney and nonkidney transplants. On univariate analysis, the risk factors for death were smoking status [OR = 4.09 (CI 95%: 1.16–14.43); $P = 0.028$] and sepsis [OR = 4.90 (CI95%: 1.39–17.31); $P = 0.014$]. Transplanted patients with AKI are younger, more prone to be diabetic and to have previous chronic renal failure compared with the general ICU population, possibly in part because of their immunosuppressive therapy. Nevertheless, they have the same prognosis.

Introduction

Transplanted patients represent a minority among the population of patients admitted to the intensive care unit (ICU) and are typically post-transplantation surgery cases. However, as the level of care continues to improve in the field of transplantation, the number of living transplanted patients is steadily increasing [1,2]. Nevertheless, these patients still represent a complex, immunosuppressed, and multi-morbid population with potential acute illness, including acute kidney injury (AKI).

It is now well-recognized that transplant patients are at higher risk (7–20%) of end-stage renal disease, often of multifactorial origin, including pre-existing renal dysfunction, hypertension, diabetes, nephrotoxicity of immunosuppression or other drugs and the occurrence of perioperative AKI [3,4].

Acute kidney injury is a common complication among critically ill patients, and two-thirds of them will require emergency renal replacement therapy (RRT) [5]. Sepsis, major surgery, cardiogenic shock and hypovolemia are the most common contributing factors to AKI. The occurrence of AKI among patients in the ICU is associated with a high hospital mortality of approximately 60% [5].

Among transplanted patients, post-transplant AKI is also associated with increased mortality [6,7], but little is

known about the overall epidemiology and prognosis of AKI requiring RRT in this population. We conducted a retrospective single center study to analyze the risk factors for AKI in this specific patient population, as well as differences in their co-morbidities and prognosis.

Methods

Patients

We retrospectively reviewed the medical records of all solid organ transplant patients admitted to the medical and surgical intensive care units (ICU), who required emergency RRT for AKI from January 1999 to May 2006 at the Geneva University Hospital in Switzerland. All the patients were treated with continuous renal replacement therapy (CRRT). This study was in accordance with the local ethics committee requirements.

Data collection

The following information was extracted from the patients' medical records: demographics, weight, co-morbidity, type of organ transplant, cardiac risk factors, pre-existing renal dysfunction, cause of AKI, immunosuppressive treatments and APACHE II. Causes of AKI were categorized into cardio-circulatory shock (including cardiogenic and hypovolemia), septic shock, nephrotoxic, acute rejection, delayed graft function, and hepato-renal syndrome.

Lengths of ICU stay, RRT days, as well as survival up to 3 months (90 days), were analyzed. Renal function measured before the AKI event was recorded, and assessed using the Cockcroft–Gault equation or through measurement of isotopic EDTA clearance. If patients had two admissions for AKI in the ICU, they were considered separately for the outcome analysis.

The results of this specific case-series population were compared with that of a cohort of critically ill patients ($n = 184$) requiring CRRT within the same time period.

Statistical analysis

The primary outcome was mortality at 90 days. For continuous variables, results are summarized as mean ± SD, or median ± interquartiles range if data distribution was abnormal; categorical variables are expressed in proportion. Comparison of continuous variables was carried out using Student's *t*-test or Mann–Whitney test. Categorical variables were compared using the chi-square or Fisher exact test. Univariate and multivariate analyses were used to assess the impact of risk factors for renal failure and co-morbidities on mortality. Two-tailed *t*-test with a $P < 0.05$ was considered as statistically significant. All data analyses were performed using SAS (version SAS 9.1.3; SAS Institute Inc.: Cary, NC, USA) and figures were produced with Prism (version 5 for Mac OS X; GraphPad Software Inc.: La Jolla, CA, USA).

Results

Over a period of 7.5 years, we identified 53 episodes of AKI requiring CRRT occurring in 51 transplanted patients, of whom 31 (58.5%) were transplanted within the preceding 48 h before their admission in the ICU. Their characteristics are summarized in Table 1. Individual solid organ transplants were: kidney ($n = 17$), liver ($n = 18$), lung ($n = 11$), heart ($n = 9$), pancreas ($n = 4$) and pancreas islets ($n = 3$). This represents a total of 62 transplanted organs. Among the subset of kidney transplants, three patients had associated pancreas islets (two had concomitant grafts), four patients had associated pancreas (three had concomitant grafts) and one patient had associated liver transplant; two lung–liver and one heart–lung transplants were noticed. Lung transplant was unipulmonar in two cases. Within the same period, the total number of transplantation in our center was 607 (41% kidney, 38% liver, 6% heart, 6% lung and 8% pancreas and islets) and the total number of CRRT intervention in ICU was 3370.

Table 1. Characteristics of the population ($n = 53$).

Age, years	50.8 ± 11.8
≤65 years, %	92.2
>65 years, %	7.8
Gender, male	38 (72)
Weight, kg	71 ± 18
APACHE II score	22 ± 8
Cardiac risk factors	
Diabetes	19 (36)
Hypertension	36 (68)
Smoker	20 (38)
Dyslipidemia	13 (25)
Type of transplantation (*n*)	
Kidney	17
Liver	18
Heart	9
Lung	11
Pancreas	4
Pancreas islets	3
Multiple	11
Transplant to admission in ICU ≤ 48 h	31 (58.5)
Kidney	9
Nonkidney	22
Transplant to CRRT ≤ 72 h	
Kidney	8
Nonkidney	13
Duration of CRRT, days	4 (2–11)
ICU length of stay, days	14 (7–30)

Values given as mean ± SD, *n* (%), or median (25–75%).

Table 2. Renal and transplantation characteristics*.

	Kidney transplants (n = 10)	Nonkidney transplant (n = 35)
Time Tpl-CRRT, days median (range)	2487 (22–7300)	10 (1–4385)
Pre-existent chronic renal failure, n (%)	4 (40)†	15 (43)
Chronic dialysis, n (%)	1 (10)	1 (3)
Calcineurin inhibitors, n (%)	5 (50)	26 (74)
Anti-thymoglobulin, n (%)	1 (10)	5 (14)

Tpl-CRRT, Time post-transplantation to initiation of CRRT.
*By episodes.
†Only patients with post-transplant chronic graft insufficiency.

Among the population of kidney transplants admitted in the ICU within 48 h post-transplantation, 8 patients had their CRRT initiated at ≤72 h. Given the difficulty to identify the onset of AKI clearly in this particular population, and the high likelihood of delayed graft function, they were excluded from further analysis.

The transplant characteristics, renal-related morbidity and potential renal toxicity related to immunosuppression regimes of the remaining 45 analyzed episodes are described in Table 2, after separation of kidney versus nonkidney transplants. Among the population of nonkidney transplants, 15 patients (43%) had pre-existent chronic renal failure (CRF), defined as glomerular filtration rate (GFR) of <60 ml/min/1.73 m^2, and one patient (lung transplant) had been intermittently on hemodialysis. Only one patient from the kidney group, who was transplanted 22 days before the initiation of CRRT, had been recently on chronic dialysis before this AKI event.

The causes of the AKI episodes are listed in Table 3. Hypovolemic shock and cardiogenic shock were grouped under cardio-circulatory. Nephrotoxic ones were contrast-related or secondary to nephrotoxic medications including calcineurin inhibitors. The majority of the episodes were a result of cardio-circulatory or septic events, and a large proportion of the AKI episodes were a result of multifactorial causes (27%). Sepsis was present in 47% of all cases. The relative proportion of oliguric patients could not be reliably determined from the patient records.

Table 3. Acute renal failure specific causes.

Etiologies	Episodes (n = 45)
Sepsis/septic shock, n (%)	21 (47)
Cardio-circulatory, n (%)	17 (38)
Nephrotoxic, n (%)	10 (22)
Hepato-renal Syndrome, n (%)	5 (11)
Multifactorial, n (%)	12 (27)

Table 4. Mortality at 90 days according to the organ transplanted.

	Survivors (n = 23)	Nonsurvivors (n = 22)
Kidney, n	6	4
Liver, n	8	10
Heart, n	3	6
Lung, n	8	3
Pancreas, n	2	0
Pancreas islets, n	1	1
Multiple, n (%)	5 (15.2)	2* (7.7)

*Kidney–islets and lung–liver.

At the time of CRRT, 62% of the patients required catecholamines support.

The mortality in the ICU and after discharge was 38% and 11%, respectively, with an overall mortality of 49% at 90 days. The mortality by organs is described in Table 4. In the nonkidney transplants, 18 of 35 patients (51%) died, with the higher proportion of death occurring in the heart transplant group (67%) and no death in the pancreas transplant group. No significant statistical difference of mortality was observed between the different types of organs transplanted ($P > 0.56$).

When survivors were compared with nonsurvivors at 90 days (Table 5), the only significant risk factors for death from univariate analysis were the smoking status [OR = 4.09 (CI 95%: 1.16–14.43); $P = 0.028$] and sepsis [OR = 4.90 (CI95%: 1.39–17.31); $P = 0.014$]. An APACHE score > 25 at entry and male gender were not predictive of higher mortality [OR = 2.25 (CI 95%: 0.68–7.47); $P = 0.18$ and OR = 4.07 (CI 95%: 0.93–17.85); $P = 0.06$ respectively].

Given the different causes and factors precipitating the AKI, no direct relationship between etiologies and mortality, except sepsis, could be found (data not shown).

Table 5. Comparison between survivors and nonsurvivors at 90 days.

	Survivors (n = 23)	Nonsurvivors (n = 22)	P-value*
Age	49 ± 12	54 ± 8	NS (0.11)
Gender (male), %	60	86	NS (0.06)
Weight	69 ± 18	74 ± 16	NS (0.33)
Diabetes, %	26	32	NS (0.75)
Dyslipidemia, %	30	14	NS (0.28)
Hypertension, %	65	59	NS (0.76)
Smoker, %	26	59	0.036
Pre-existent chronic renal failure, %	65	45	NS (0.24)
Kidney transplants, %	26	18	NS (0.72)
APACHE II	23 ± 8	25 ± 10	NS (0.11)
Sepsis, %	30	68	0.017

*Student's t-test and Fisher's exact test.

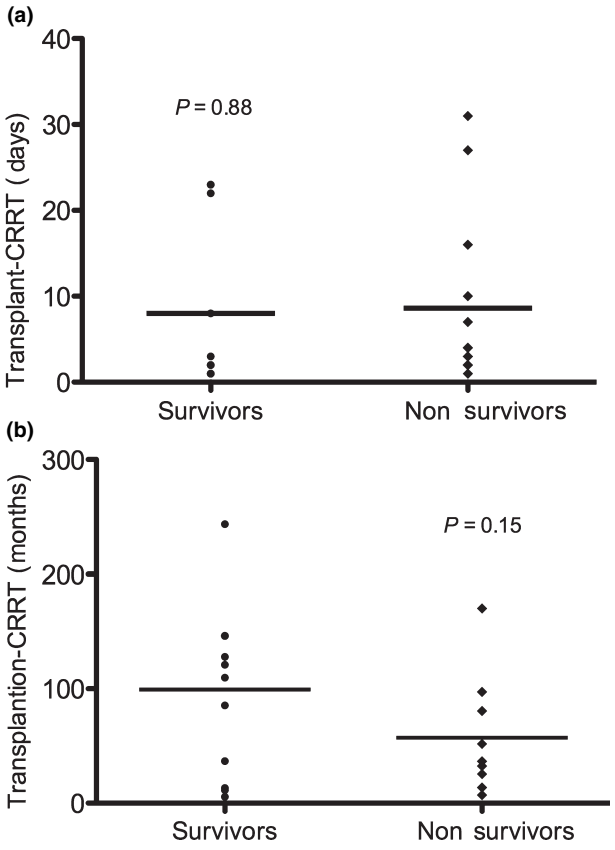

Figure 1 Survival related to post-transplantation time to CRRT. (a) Post-transplantation time to CRRT ≤ 31 days. (b) Post-transplantation time to CRRT > 31 days. A comparative study (a) Early transplanted group (≤31 days): the mean time (days) from transplantation to CRRT for survivors versus nonsurvivors (8 ± 2.9 vs. 8.6 ± 2.7) is not statistically different. (b) Late transplanted group (>31 days): the mean time (months) from transplantation to CRRT for survivors versus nonsurvivors (99.2 ± 20.7 vs. 57.2 ± 17.3) is not statistically different.

A logistic regression was carried out, first including only the variables with a *P*-value <0.2, and then with all of the clinically relevant variables entered into the multivariate model. The analysis was fit to evaluate the odds ratio and their 95% CI for patients' death at 90 days. No significant independent predictor was found. For the two patients who sustained two distinct AKI episodes requiring RRT, we were able to analyze these as independent events, given the long interval between the two episodes (>6 months).

An important parameter observed in our cohort was the difference in the post-transplantation time before the occurrence of the AKI (defined as initiation of CRRT). We identified two clusters of patients: one group of early transplanted, within 31 days (range 1–31 days), and one group of late transplanted, with a longer transplantation duration (range 5.3 to 243.3 months). No statistical

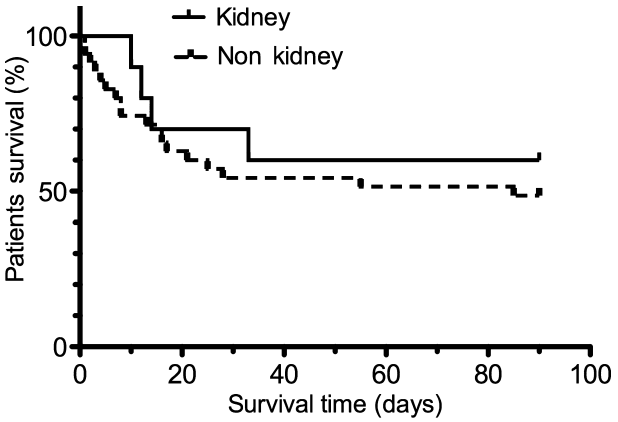

Figure 2 Kaplan–Meier survival curve. Estimation of survival up to 90 days, comparing kidney with nonkidney transplants.

difference regarding the proportion of nonsurvivors was noted between early and late transplanted groups (OR = 1.58 [CI 95%: 0.48–5.13]; *P* = 0.55). The mean post-transplantation times were not different for survivors versus nonsurvivors, within the groups (Fig. 1a: group ≤ 31 days and b: group > 31 days).

After separation of the kidney versus nonkidney transplants, a survival curve estimate was created, representing the survival time from CRRT initiation, up to 90 days (Fig. 2). No difference could be detected on Log Rank test, between the two survival curves [HR = 0.71 (CI 95%: 0.27 to 1.88); *P* = 0.49] or on Cox hazard regression [HR = 0.69, (CI 95%: 0.12–3.87); *P* = 0.67], after adjustment for age, gender, smoking and sepsis.

Regarding the renal function outcome when considering only the nonkidney transplant survivors (*n* = 17), we assessed their creatinine levels at 3 months and the necessity for ongoing renal replacement. The records of three patients were not available at the time of assessment, because their follow-up was carried out in other centers. Compared with the previous creatinine level, 6 of 14 patients (43%) returned to their previous level (tolerance of ±10% variation), while 8 (57%) did not recover their previous renal function. Of the latter, three patients had to be on long-term hemodialysis.

Discussion

The purpose of this small retrospective series was to describe the morbidity and mortality of a specific population of solid organ transplants, requiring CRRT for AKI. Our measured mortality rate of 49% at 90 days is within the range (39–71%) reported by the literature for general ICU patients [5,8]. We excluded the kidney transplanted patients who were given RRT within 72 h from our analysis, because of the difficulty in defining the cause of

AKI in them; CRRT was generally initiated for delayed graft function and fluid overload, which are usually not associated with high morbidity and mortality.

Mortality related to AKI represents an important morbidity within hospitalized patients, especially in the transplanted population, as they are more prone to pre-existing renal failure related to a broad spectrum of renal disorders [9]. Transplant patients are a growing population, and exhibit an incidence of 20–60% peri-transplantation AKI [10]. The need for CRRT in 10–25% of these patients is a strong outcome predictor, and renal function deterioration is a growing long-term morbidity in this population [4].

Most investigations in the literature have focused on the long-term outcome of chronic renal failure, [4,11] and few have looked at AKI, generally focusing on peri-operative (peri-transplantation) events [6,7]. Very rare series have addressed the problem of acute kidney injury requiring CRRT among transplanted population and even the incidence of AKI among the transplant population is not well studied. A cohort from a transplanted population database in New York revealed an incidence of a certain degree of acute renal failure in 25% of the patients, with 8% of them requiring renal replacement therapy [10].

Intriguingly, the only series comparing AKI in nonrenal transplant patients with that in nontransplant patients found a significantly lower mortality for the former (34.7% vs. 61.9%) [12]. This difference was related to the sub-groups requiring RRT, increasing the mortality particularly within the nontransplant population. This is explained by the fact that part of the transplant population, requiring RRT for fluid overload, is less severely ill.

During the first half of the period of our retrospective analysis, a large cohort of critically ill patients sustaining CRRT for AKI admitted to our center was studied [13]. We compared our transplant series with this cohort, after retrieving the transplanted patients already selected in our series (Table 6).

In this prospective trial comparing two doses of dialysis, the overall mortality at 90 days was 49%, and 75% of survivors had recovered their previous renal function. Transplanted patients were found to be younger, male in majority, and having more diagnosed cases of diabetes. Pre-existing renal failure prevalence was higher (55% vs. 29%; $P = 0.0015$).

In terms of the relation to mortality, our results are difficult to appreciate in such a small heterogeneous population, in the absence of the precise indications for the initiation of RRT, and because of confounding factors, including various causes of AKI, differing severity of illness, and multiple co-morbidities. We were unable to find any relation between the post transplantation time prior to the initiation of the RRT and mortality at 90 days.

Table 6. Characteristics comparison between transplanted and non-transplanted population.

Variables	Transplants (n = 45)	Nontransplants (n = 184)	P-value†
Age, years	51.7 ± 10.7	64 ± 14	<0.0001
Gender, male	33 (73)	78 (42)	0.0002
Weight (Kg)	72 ± 17	73.6 ± 17.5	NS
Pre-existing CRF	25 (55)*	54 (29)	0.0015
Diabetes	13 (29)	31 (17)	0.025
APACHE II	23 ± 9	25 ± 9	NS
ICU LOS, days	16 (7–31)	6 (3–14)	<0.0001
CRRT duration, days	5 (3–13)	3 (2–5.5)	0.0023
Sepsis	21 (46.6)	115 (62.2)	NS
90 days mortality	22 (49)	91 (49)	NS

Values given as mean ± SD, n (%), or median (25–75%).
CRF, chronic renal failure; LOS, length of stay.
*Recent renal transplantation in one patient.
†Student's t-test, Fisher's exact test and Mann–Whitney test, as appropriate.

However, the presence of sepsis and being a smoker were related to higher mortality, at least in the univariate analyses. The statistical significance was lost after the inclusion of covariates in the analysis. Compared with the cohort of AKI requiring RRT during the same period, the mortality was similar.

In regard to the risk for AKI, our population had an important pre-existing renal dysfunction rate. Within the nonkidney transplants, 44% had pre-existent chronic renal failure, which poses considerable risk for an acute oliguric phase and the need for RRT. Other co-morbidities, such as cardiac risk factors, were pre-eminent, especially hypertension and diabetes. These co-morbidities promote the development of renal ischemia through transient renal hypoperfusion, and this was likely in patients with cardio-circulatory, septic and hepato-renal causes of AKI.

In sepsis, 23–51% of patients can develop AKI, depending on the severity of illness [14], as was found in the largest series on AKI in critically ill patients to date [5,15]. Septic shock is then recognized to be the most common contributing factor to AKI and mortality, an observation that we also made in this series.

The limitations of our study are the retrospective nature of data collection, the heterogeneity in the levels of disease severity and in our population, the heterogenic nature of the groups (post-op renal failure, transplanted with acute event on pre-existing renal failure), and the unmeasured variability of the indicators for CRRT in our population (BUN level, fluid overload and delayed graft function). Finally, because of the heterogeneity of immunosuppressive regimens, we were not able to stratify the patients according to their immunosuppressive treatment

and identify any association between immunosuppressive drugs and risk of AKI.

However, few observations can be drawn from our analysis. The main factors predisposing renal failure in recent transplant patients are related to their pre-existing renal dysfunction and underlying cardio-circulatory or hepatic insufficiency. Ischemia/reperfusion injury throughout organ donation to engraftment plays an important role in peri-transplantation AKI. Transplanted patients with AKI are younger, and more prone to be diabetic and to have previous chronic renal failure, possibly in part as a result of their immunosuppressive therapy. Nevertheless, the incidence of sepsis is not increased in our transplant population while being treated with immunosuppressive drugs; this is likely because of the small sample and the high incidence of sepsis which is a main contributing factor to AKI in the general ICU population [5]. Despite the illness being less severe in terms of their APACHE score, transplanted patients had a longer ICU length of stay and often required a longer duration of CRRT, which ultimately increases the cost of caring for this population of patients, and increases their burden on the health care system [16].

Conclusion

Transplanted patients with AKI represent a young population, more prone to be diabetic and to have previous chronic renal failure than the general ICU population, possibly in part as a result of their immunosuppressive therapy. According to our data, despite their polymorbidity, their immunosuppression and longer length of stay, patients requiring RRT have the same prognosis as the general ICU population. The initial severity of illness and the presence of sepsis remain the most important morbidity factors.

Though the retrospective design of our study does not exclude a selection bias, these data support the intensive use of RRT in the transplanted population, even in the presence of multiple organ failure.

Better prospective epidemiological studies, focusing not only on peri-transplantation, but also on 'at distance' AKI among these highly polymorbid patients, might help to improve preventive measures or therapeutic interventions in this increasing ICU subpopulation.

Authorship

EC, PS: performed research/study, collected data, analyzed data and wrote the paper. PAT, GM and PYM: contributed to the collection and analyses of data, as well writing of the paper. KQ: contributed to the writing of the paper.

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