# Survival analysis and associated factors to mortality of renal transplant recipients in a University Hospital in Maranhão

**Authors**
Maria Inês Gomes de Oliveira[1]
Alcione Miranda dos Santos[2]
Natalino Salgado Filho[3]

[1] MSc (Assistant physician).
[2] PhD (Professor of the Federal University of Maranhão).
[3] PhD (Dean of the Federal University of Maranhão).

Submitted on: 12/30/2011.
Approved on: 05/11/2012.

**Correspondence to:**
Maria Inês Gomes de Oliveira.
Hospital Universitário da Universidade Federal do Maranhão - HUUFMA.
Transplante Renal.
Rua Barão de Itapary, nº 227, 2º andar. São Luís, MA, Brazil.
CEP: 65070-905.

## ABSTRACT

**Introduction:** Renal transplantation is regarded as the best treatment for patients with Chronic Kidney Disease. Factors associated to survival of renal transplant recipients must be evaluated in order to implement appropriate conducts in these patients. **Aims:** To analyze the renal transplant patients survival and associated factors to their mortality. **Methods:** Observational, retrospective cohort study, including all the 215 patients who underwent kidney transplantation in the Renal Transplant Service of the Hospital Universitário da Universidade Federal do Maranhão (HUUFMA), from March 18, 2000 to September 18, 2008, with a follow-up ranging from 12 to 101 months. Demographic and clinical characteristics were observed. The Kaplan-Meier method was used for construction of survival curves, and they were compared by log-rank test. The Cox proportional hazards model was used for identification of factors associated to mortality. **Results:** The prevalence of deaths was 10,6%. The survival rates at 1, 3 and 5 years for living donors recipients were 97,8%, 94,1% and 92,9%, respectively and for deceased donors recipients, 95,6% and 95,6%, at 1 and 3 years, respectively. Factors statistically associated to a lower survival were: recipient age above 40 years (RR = 6.19; $p$ = 0.001; 95% CI = 2.01-18.99) and surgery complications (RR = 4.98; $p$ = 0.041; 95% CI = 1.07-23.27). **Conclusions:** Kidney recipients survival rates at HUUFMA were similar to the rates related in other, Brazilian and international studies. Recipient age above 40 years and surgery complications were significantly associated to mortality in this study.

**Keywords:** kidney transplantation, mortality, risk factors, survival.

## INTRODUCTION

Kidney transplantation (KT) is an ideal therapeutic approach for most patients with terminal chronic kidney disease (CKD), as it improves quality of life, reduces mortality, and offers a higher life expectancy when compared to dialysis.[1] This holds true even when considering certain patient groups, such as diabetics and the elderly, for whom such procedures were not permitted in the past.[2]

With improvements in immunopharmacology and the clinical handling of patients, a decrease in the mortality rate after KT has been observed over time, although this decrease has not been followed by changes in the causes of death in this population. Cardiovascular diseases (CVD) have maintained their status as the main cause of death after KT.[3]

The prevalence of cardiovascular risk factors is high among KT recipients; many recipients present with prior CVD, diabetes mellitus (DM), hypertension (H), or dyslipidemia at the time of the transplant[4], and these patients have an annual risk of 3.5-5% for CVD-related death.[5]

Infections are important risk factors for mortality in KT recipients, who are susceptible to a large variety of pathogens, particularly bacteria, fungi, and viruses, as a consequence of immunosuppressive therapy.[6] This immunosuppression-infection binomial frequently implies an impaired inflammatory response in the host, making it difficult to diagnose the infectious process and delaying adequate treatment for reducing the associated morbimortality.[7] Additionally, some infections,

particularly by viruses, may contribute to dysfunction and/or rejection of the graft and the development of systemic diseases and some neoplasms.[6]

Malignant neoplasms are responsible for a high proportion of late mortality cases following KT, varying between 10% and 47%; survival increases both after transplantation and during the follow-up period.[8]

The main objective of this study was to identify the factors that had an impact on the survival of patients that underwent KT at the Kidney Transplant Center of the University Hospital of the Federal University of Maranhão (HUUFMA) between March 18, 2000 and September 18, 2008.

## Methods

The study was a retrospective cohort observational assessment study. All 215 patients who underwent KT at HUUFMA between March 18, 2000 and September 18, 2008, with a live or deceased donor of any age or sex, with a minimum follow-up period of 12 months and a maximum follow-up period of 101 months, were analyzed. The study was conducted between January 2008 and December 2009.

Demographic, clinical, laboratory, pretransplantation, and evolutionary clinical data after KT were obtained from patient records.

The definitions used in the study are as follows: H, systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg;[9] anemia, hemoglobin level < 12 g/dL or use of recombinant human erythropoietin;[10] hypercholesterolemia, total cholesterol level ≥ 200 mg/dL;[11] hypertriglyceridemia, triglyceride level > 150 mg/dL;[11] hyperuricemia, uric acid level > 7 mg/dL;[12] obesity (defined according to the classification by the World Health Organization [WHO]),[13] body mass index (BMI) ≥ 30 kg/m$^2$; left ventricular hypertrophy (LVH; defined according to the criteria of the American Society of Echocardiography [ASE]), normal values of the left ventricle mass index of up to 110 g/m$^2$ for women and up to 134 g/m$^2$ for men;[14] induction, use of intense immunosuppression in the initial stages of the transplant with the goal of immediately decreasing the immune response to the allograft;[15] monoclonal-anti interleukin-2 (IL-2), basiliximab, and polyclonal, antithymocyte globulin (ATG) antibodies (used in moderate-to-high immunological risk patients according to the center criteria); surgical complications, surgical complications of any etiology, which presented at any time after the transplant.

Standard antibiotic prophylaxis using cefazolin was conducted for all surgical procedures.

Numerical variables are presented as mean and standard deviation (mean ± SD), and categorical variables are presented as frequency and percentage.

Patient age was categorized as ≤ 40 years and > 40 years. Dialysis time was categorized as ≤ 3 years and > 3 years. These categories were determined by the mean values of each of the 2 variables in order to calculate risk ratios (RRs).

Comparisons between the demographic and clinical characteristics of the patients who died and those of the patients who survived were conducted using the chi-squared (chi$^2$) test of association or, when indicated, Fisher's exact test.

Survival was analyzed considering follow-up time, that is, the time (in months) between the transplant date and death directly or indirectly attributed to KT. Patients who experienced kidney graft loss, died due to external causes, or were alive until the end of the study were excluded.

Survival curves stratified according to the demographic and clinical characteristics of the patients were calculated by the Kaplan-Meier method and the differences between the curves were assessed using the bilateral log-rank test.

To identify the factors linked to mortality, the Cox proportional hazards model was used.[16]

The variables with a p value of < 0.20 in the univariate analysis or those with a p value ≥ 0.20, yet clinically significant according to the literature, were included in the multivariate analysis. Only the variables with *p*-values of < 0.05 remained in the final model. The RRs and its respective 95% confidence intervals (CIs) were also estimated.

Statistical analyses were conducted using the Stata version 10.0 statistical package (StataCorp, College Station, TX, USA). In all of the analyses, a significance level of 0.05 was considered.

In compliance with the requirements of Resolution 196/96 and complements of the National Board of Health, this study was approved by the Research Ethics Committee of the HUUFMA, under protocol nº 004448/2008-60 and decision nº 272/2008.28.

## Results

Throughout the study period, 215 kidney transplants were performed at our center, all of which were included in the review.

A comparison of the demographic characteristics of the patients who died with the characteristics of the surviving patients is shown in Table 1. Mixed race (64.7%) and male gender (55.3%) were the most prevalent characteristics; however, there was no statistically significant difference between these 2 groups in this regard. Additionally, no significant differences were observed with regard to underlying disease, dialysis time, type of donor, and induction therapy (Table 1).

The "others" group covered, overall, 18% of the underlying diseases (38/215) and included systemic lupus erythematosus (SLE; 12/38), urological causes (8/38), genetic diseases (7/38), autosomal polycystic kidney disease (APKD; 5/38), nephritis (4/38), and traumatic nephrectomy on a single kidney (2/38). In 105 patients (48.8%), the CKD etiology was not specified. DM was the cause of CKD in 7.4% of our study cohort (Table 1).

Most patients showed a prior dialysis time of ≤ 3 years, both in the death group (72.7%) and the survival group (72.0%; $p = 0.94$). The average dialysis time in the death group was 35.9 months (0–120 months) and that of survivors was 32.5 months (0–142 months; data not shown).

There was a predominance of KT from live donors (87%).

Induction immunosuppressive therapy was used in 49 patients (23%), of which 34 (69%) were treated with basiliximab and 15 (31%) with ATG. However, no significant link to death and infectious diseases, CVD, or other causes was demonstrated in the comparison between the death and survivor groups ($p = 0.78$). On the other hand, the association between induction and the type of donor was statistically significant ($p < 0.001$); ninety-six percent of the transplants from deceased donors received induction vs. 13% of those from a live donor (data not shown).

The initial immunosuppressive regimens included, in total (n = 215), a calcineurin inhibitor (CIN) in combination with a corticosteroid and an antiproliferative agent; Thirty-five percent included cyclosporine A (CsA) + prednisone (Pred) + azathioprine (Aza); 27% included CsA + Pred + mycophenolate mofetil (MMF); and 31% included tacrolimus (Fk) + Pred + MMF; and 7% included Fk + Pred + Aza. The most commonly used maintenance immunosuppressive regimens in this study were as follows: Fk + Pred + MMF (20%), sirolimus + Pred + MMF (17%), CsA + Pred + MMF (10%), CsA + Pred + Aza (6%), and Pred + Aza (5%).

The average age in this series was 35.6 (± 13.4) years for the recipients and 37.8 (± 10.0) years for the donors. With regard to age, 77.3% of the KT recipients

**Table 1** Characteristics of kidney transplant patients at HUUFMA, between 03.18.2000 and 09.18.2008

| Variables | Deaths | | Survivors | | *p* |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Age (years)** | | | | | |
| > 40 | 17 | 77.3 | 70 | 36.3 | 0.001 |
| ≤ 40 | 5 | 22.7 | 123 | 63.7 | |
| **Race** | | | | | |
| White | 7 | 31.8 | 28 | 14.5 | 0.11 |
| Mixed | 12 | 54.6 | 127 | 65.8 | |
| Black | 3 | 13.6 | 38 | 19.7 | |
| **Sex** | | | | | |
| Male | 14 | 63.6 | 105 | 54.4 | 0.41 |
| Female | 8 | 36.4 | 88 | 45.6 | |
| **Underlying disease/** | | | | | |
| CGN* | 3 | 13.6 | 25 | 13.0 | |
| Hypertensive nephrosclerosis | 5 | 22.7 | 23 | 11.9 | 0.22 |
| DM** | 3 | 13.6 | 13 | 6.7 | |
| Unspecified | 6 | 27.3 | 99 | 51.3 | |
| Other | 5 | 22.7 | 33 | 17.1 | |
| **Dialysis time (years)** | | | | | |
| > 3 years | 6 | 27.3 | 54 | 28.0 | 0.94 |
| ≤ 3 years | 16 | 72.7 | 139 | 72.0 | |
| **Donor type** | | | | | |
| Live | 19 | 86.4 | 168 | 87.1 | 0.93 |
| Deceased | 3 | 13.6 | 25 | 12.9 | |
| **Induction** | | | | | |
| Yes | 6 | 27.3 | 43 | 22.3 | 0.60 |
| No | 16 | 72.7 | 150 | 77.7 | |
| **Surgical complication** | | | | | |
| Yes | 16 | 72.7 | 65 | 33.7 | < 0.001 |
| No | 6 | 27.3 | 128 | 66.3 | |
| **Reoperation** | | | | | |
| Yes | 13 | 59.1 | 54 | 28.0 | 0.003 |
| NO | 9 | 40.9 | 139 | 72.0 | |

*CGN: chronic glomerulonephritis; **DM: diabetes mellitus.

who died were aged > 40 years, while 36.3% of the survivors were in this age group; this difference was statistically significant ($p < 0.001$; Table 1).

Surgical complication ($p < 0.001$) and reoperation ($p = 0.003$) also showed statistically significant differences between the 2 groups.

Of the 81 patients with surgical complications (Table 1), 87.6% received grafts from live donors (71/81) and 22.2% (18/81) received induction; these factors did not obtain statistical significance ($p = 0.82$ and $p = 0.88$, $chi^2$, respectively).

In the death group, 16 patients had surgical complications (Table 1), which were the direct causes of death in 9 cases (56.3%). Only 1 patient received a transplant from a deceased donor. The main surgical complications in the death group were as follows: kidney graft rupture/arterial thrombosis (31.3%, 5/16), urinary fistula (18.7%, 3/16), acute obstructive abdomen (6.2%, 1/16), colelithiasis (6.2%, 1/16), incisional hernia (6.2%, 1/16), and surgical wound dehiscence (6.2%, 1/16). Eighty-one percent of the patients required reoperation, and the surgery was directly related to the transplant in 10 patients (77%). In the other 3 patients (3/16), the reintervention was due to other surgical pathologies, including colelithiasis (27 months after transplant), pleural empyema (after 23 months), and intestinal obstruction (after 4 months).

Kidney graft function loss occurred 45 patients (20.9%), and the most frequent causes were death of the functioning graft (38%); chronic graft nephropathy (CGN; 31%), and acute rejection (AR; 13%). The CGN and AR diagnoses were confirmed through biopsy, and cell-mediated rejection was prevalent (data not shown).

With regard to human leukocyte antigen (HLA) types, 64% of the transplant patients showed haploidentical (47%) or identical (17%) typing results (data not shown).

Death following KT occurred in 22 patients (10.6%); the average survival time of these patients was 14.4 (± 16.4) months. Among these patients, 12 (54.5%) died in the first year after the transplant, with 10 deaths occurring in the first 6 months (45.4%). Only 1 patient (4.5%) died 5 years after the transplant; the remaining 9 patients (40.9%) died after the first year and before the 5-year anniversary of the transplant.

Table 2 shows the causes of death. Infectious conditions were the most frequent cause (60%), followed by cardiovascular, cerebrovascular, and peripheral vascular complications (22%).

**Table 2** Causes of death in renal transplant patients at HUUFMA, between 03.18.2000 and 09.18.2008

| Causes of Death | Frequency | % |
|---|---|---|
| Septic shock | 11 | 50 |
| Cerebral toxoplasmosis | 1 | 5 |
| Complicated varicella | 1 | 5 |
| Cardiovascular disease* | 5 | 22 |
| Hypovolemic shock | 3 | 13 |
| Lung cancer | 1 | 5 |

*Including acute myocardial infarction (AMI), cerebrovascular accident (CVA), deep vein thrombosis (DVT), and pulmonary embolism (PE).

Among the infection-related deaths, 84.6% (11/13) were due to septic shock, 7.7% were due to cerebral toxoplasmosis, and 7.7% were due to complications from varicella. Among the 13 deaths attributed to infections, 10 (76.9%) occurred in patients who showed some type of surgical complication; among these patients, 9 (69.2%) underwent reoperation. Septic shock was responsible for half of the deaths occurring in the first year post-transplant (6/12), of which 5 cases (45.4%) were secondary to surgical reintervention.

There was only 1 death due to neoplasm (lung cancer), which occurred in the 34th month after the KT.

Table 3 shows the comorbid conditions of the patients. There was no significant difference between the 2 groups with regard to any comorbidity. The most prevalent conditions in the death and survivor groups, respectively, were H (73% vs. 86%, $p = 0.10$), hypertriglyceridemia (41% vs. 53%, $p = 0.27$), and DM (27% vs. 29%, $p = 0.86$). In the death group, DM was present in almost a third of the patients, and the deaths were related to infection in all 6 cases; of these patients, 67% (4/6) died in an average period of 159 (± 124) days. Only 1 of these patients received a graft from a deceased donor (1/6).

The clinical complications following KT are shown in Table 4 and include both immunological and non-immunological conditions. None of these complications obtained statistical significance in the comparison between the groups. The most prevalent infections were those of the urinary tract (UTI), bacterial and fungal, in the airways, herpes simplex, and varicella-zoster (data not shown).

**Table 3** Comorbid conditions of renal transplant patients at HUUFMA, between 03.18.2000 and 09.18.2008

| Comorbidities | Deaths | | Survivors | | *p* |
|---|---|---|---|---|---|
| | n | % | n | % | |
| H* | 16 | 72.7 | 166 | 86.0 | 0.10 |
| DM** | 6 | 27.3 | 56 | 29.0 | 0.86 |
| Anemia (Hb ≤ 12 g/dL) | 5 | 22.7 | 58 | 30.1 | 0.47 |
| Total triglycerides > 150 mg/dL | 9 | 40.9 | 103 | 53.8 | 0.27 |
| Total cholesterol ≥ 220 mg/dL | 5 | 22.7 | 56 | 29.0 | 0.53 |
| Uric acid > 7 mg/dL | 3 | 13.6 | 28 | 14.5 | 0.91 |
| HCV*** | 2 | 9.1 | 11 | 5.7 | 0.53 |
| Obesity (BMI ≥ 30 kg/m$^2$ | 0 | 0 | 14 | 7.3 | 0.19 |
| LVH*** | 3 | 13.6 | 29 | 15.0 | 0.86 |

*H: arterial hypertension; **DM: diabetes mellitus; ***HCV: hepatitis C virus; ****LVH: left ventricular hypertrophy.

**Table 4** Post kidney transplant complications at HUUFMA, between 03.18.2000 and 09.18.2008

| Post-transplant clinical complications | Deaths | | Survivors | | *p* |
|---|---|---|---|---|---|
| | n | % | n | % | |
| PTDM* | 3 | 13.6 | 43 | 22.3 | 0.35 |
| CAD/AMI♣ | 3 | 13.6 | 8 | 4.1 | 0.06 |
| CVA° | 2 | 9.1 | 4 | 2.1 | 0.06 |
| Acute rejection | 5 | 22.7 | 69 | 35.7 | 0.22 |
| CGN• | 4 | 18.2 | 57 | 29.5 | 0.26 |
| CGN relapse+ | 1 | 4.5 | 9 | 4.7 | 0.98 |
| Nephrotoxicity | 5 | 22.7 | 66 | 34.2 | 0.28 |
| Infection | 16 | 72.7 | 169 | 87.5 | 0.06 |
| Malignant neoplasm | 2 | 9.1 | 9 | 4.7 | 0.37 |

* PTDM: post-transplant diabetes mellitus; ♣ CAD/AMI: coronary artery disease/acute myocardial infarction; ° CVA: cerebrovascular accident; • CGN: chronic graft nephropathy; + CGN relapse: chronic glomerulonephritis.

The survival rates of patients that received grafts from live donors 1, 3, and 5 years after the transplant were 97.8%, 94.1%, and 92.9%, respectively. For those that received transplants from deceased donors, the survival rates for 1 and 3 years were 95.6% and 95.6%, respectively.

The differences in the survival rate between the groups that received transplants from live and deceased donors were not statistically significant for any of the periods taken into consideration, e.g., 1 year ($p$ = 0.52) and 3 years ($p$ = 0.69).

Table 5 shows the univariate analysis results with RRs and the respective 95% CIs. In patients aged > 40 years, surgical complications and reoperation were statistically significant factors, which were included in the multivariate analysis. After an adjusted analysis, the factors linked to decreased patient survival that remained were as follows: age > 40 years (RR = 6.19, $p$ = 0.001, 95% CI = 2.01–18.99) and surgical complications (RR = 4.98, $p$ = 0.041, 95% CI = 1.07–23.27).

**Table 5** Factors linked to renal transplant patient survival at HUUFMA, between 03.18.2000 and 09.18.2008

| Variables | Relative Risk | *p* | 95% Confidence Interval |
|---|---|---|---|
| Age > 40 years | 7.08 | < 0.001 | [2.38; 21.06] |
| Surgical complication | 5.64 | 0.001 | [2.06; 15.39] |
| Reoperation | 3.92 | 0.002 | [1.62; 9.46] |
| CAD/AMI* | 2.96 | 0.082 | [0.87; 10.07] |
| CVA** | 3.69 | 0.079 | [0.86; 15.88] |
| Infection | 0.43 | 0.103 | [0.16; 1.18] |

* CAD/AMI: coronary artery disease/acute myocardial infarction; ** CVA: cerebrovascular accident.

Figure 1 shows the survival curves of the variables that remained significant in the adjusted analysis. Recipients > 40 years of age showed lower survival rates relative to younger recipients ($p$ = 0.001). The same result was observed for those who presented surgical complications ($p$ = 0.041).

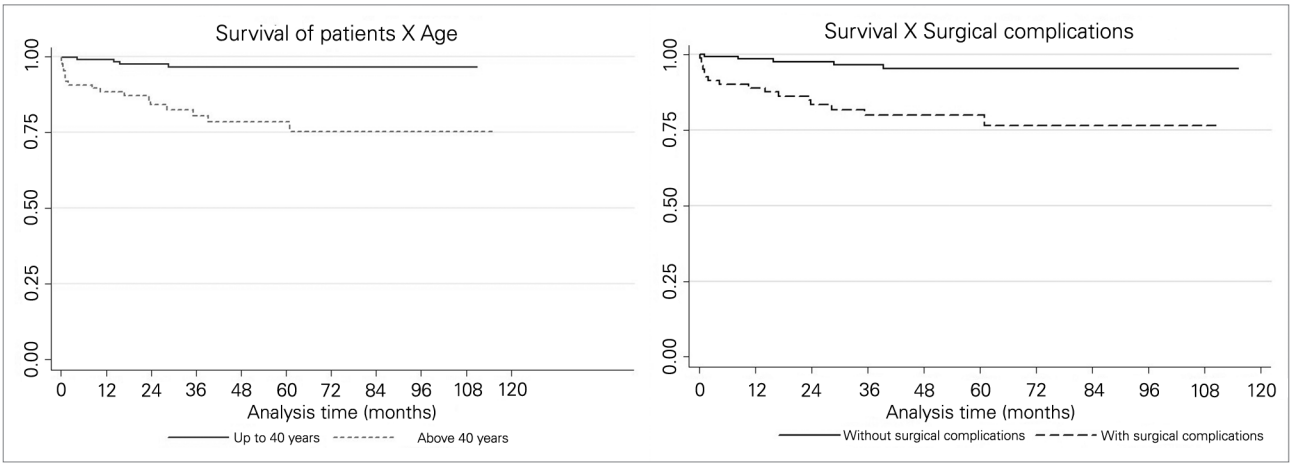
## Discussion

In this study, the demographic and clinical characteristics of 215 patients who underwent KT at HUUFMA over an 8-year period were analyzed.

In approximately half of the patients in the present study, the underlying disease was unspecified, as reported in several studies.[17-19] This situation is common and may represent a failure of the health system in terms of early detection and adequate handling of CKD, even when considering a future post-transplant follow-up.

Most deaths (12/22) occurred in the early period after the KT (< 1 year), and half of these deaths were the result of septic shock (6/12). In São Paulo, De Marco *et al.*[20] reported a mortality rate of 78.5% due to septic shock in a group of 14 KT recipients (May 2000 to

**Figure 1.** Patient survival curves.




December 2001), of which 11 were in the first year post-transplant. In our study, infectious complications were the most prevalent causes of death at any time after the transplant (60%), followed by cardiovascular, cerebrovascular, and peripheral vascular causes (22%). These findings are in line with the data in the literature, in varied proportions.[3,17-19,21,22] Linares *et al.*[21] reported mortality rates due to CVD of 38%, 29% due to infection, and 12% due to neoplasm in a cohort of 1,218 KT recipients between 1995 and 2004 in Spain. In our country, as well as in other developing nations such as Thailand[17] and India,[22,23] mortality associated with infection after KT shows a greater impact in relation to all other causes of death. This may be explained by the unfavorable social and economic conditions that exist in a large portion these areas, climatic conditions, and the coexistence of endemic diseases.

A study that included 1,676 kidney transplant patients conducted between January 1998 and March 2004 at the Kidney and Hypertension Hospital and the São Paulo Hospital showed a 49% prevalence of infectious complications in the first year after transplantation, notably respiratory, herpetic, and UTIs.[19] In our study, these were also the most prevalent infections.

Several studies have linked pre-transplant dialysis time to negative post-transplant outcomes[5,24-26]. Cosio *et al.*[24] assessed the impact of this factor on patient survival, with an 84 ± 14-month follow-up, by comparing 3 groups: the first without prior dialysis (preemptive), the second with a time of up to 2 years in dialysis, and the last group with 3 years of dialysis; the mortality rates reported were 7%, 23%, and 41%, respectively. In their multivariate analysis, patient survival rates differed significantly between the 3 groups. Goldfarb-Rumyantzev *et al.*[25] concluded that a prolonged dialysis time is linked to unsatisfactory outcomes, both for the graft and the survival of the patient following the KT.

In our study, the average dialysis time was 32.9 (± 30.3) months, and there was no statistically significant association between dialysis time and mortality following the KT. Arend *et al.*,[26] in the Netherlands, and Kimura *et al.*,[27] in Japan, did not report an association between these factors either.

At HUUFMA during the study period, 87% of the transplants were obtained from live donors, possibly due to the lack of an effective policy for transplants in the State, which can be well demonstrated by the numbers of the Brazilian Transplant Records (*RBT*) of the Brazilian Association of Organ Transplant (ABTO).[28] However, in Brazil as a whole, the number of KTs obtained from deceased donors has only surpassed the number of live donors as of 2008.[29] According to the most recent Brazilian Transplant Records, the number of deceased donors in Maranhão was greater than the number of live donors in 2008, 2009, and 2011.[28,30,31] In our State, all of the steps of the donation-transplant process lack a structure that allows for a more effective operation. Such unfair distribution of the transplantation activity in Brazil is due to the great structural differences between the many regions of the country.[28,29]

In this work, there was no significant association between induction therapy and mortality by any cause ($p$ = 0.78, chi$^2$). Twelve percent (6/49) of the patients who received induction died: 4 due to infections, 1 due to cerebral vascular accident, and 1 due to hypovolemic shock. However, considering that less than a third

of the patients received induction, the apparent lack of such a link to mortality is not consistent. According to Meier-Kriesche *et al.*[32], induction of treatment with antibodies represents a significant risk of late death in general (RR = 1.1, $p < 0.001$). For deaths occurring up to 6 months post-transplant, the risk is also significant in the case of death by infection (RR = 1.32, $p < 0.001$) and CVD (RR = 1.27, $p < 0.001$).[32]

In our study, H was present in 72.7% of the patients who died and 87.5% of the surviving patients ($p = 0.06$). H is considered the most important cardiovascular risk factor in this population. According to Ojo,[5] H is present in more than half of dialysis patients, and after transplantation, it affects 75–90% of the recipients, which is in agreement with our findings. H results particularly from the condition of H prior to transplantation and the addition of CIN after the transplant as a maintenance immunosuppressant. Shirali & Bia[33] stated in 2008 that CIN, especially CsA, contributes to H through vasoconstriction and saline retention mechanisms. In our study, all 182 patients with H used at least 1 CIN as an initial immunosuppressant; among these patients, 113 (62%) used cyclosporine, which was significantly associated with H ($p = 0.009$, chi$^2$). Marcén[34] stated that any immunosuppressant regimen should maximize graft survival and minimize rejection, nephrotoxicity, cardiovascular risk, and other adverse effects. Thus, CIN and corticosteroids have an important impact on cardiovascular risk such as an increase in the severity of H, dyslipidemia, and DM.

The presence of DM constitutes, in many studies,[3,5,32,34-36] an independent risk factor for patient survival after KT since it increases cardiovascular risk. In our case series, 28.8% of the patients were diabetic (7.4% from underlying diseases and 21.4% with post-transplant DM); when comparing deaths vs. surviving patients (27.3% vs. 29.0%, respectively, $p = 0.86$), DM did not significantly impact the survival of the patients, which contradicts the data in the literature. Approximately 10% of our diabetic patients died (6/62) in the same proportion as those who died and were not diabetic (16/153). In patients with DM, the deaths were linked to infections in all 6 cases and not to CVD.

Cosio *et al.*[36] reported that the recipients with DM show a significantly higher mortality rate linked to CVD and infection, but not to malignancy, when compared to nondiabetics. Similarly, Soveri *et al.*[37], over a 5-year follow-up period, reported an all-cause mortality rate of 10.4% in nondiabetics and 24.6% in diabetics ($p < 0.0001$). Orsenigo *et al.*[35], in a multivariate analysis of the factors affecting graft and patient survival after KT, identified DM and age of the recipient as significant predictors of mortality in the final model.

The age of the recipient has been reported as the main determinant in KT outcomes.[35,38] In our study, 77.3% of the patients who died were aged > 40 years, and the relative mortality risk was 6.19 for these patients. This finding is similar to that of Arend *et al.*,[26] in the Netherlands, who determined that in a cohort of 1002 patients, the relative mortality risk is greater in patients aged > 40 years after the first transplant. Similarly, Gentil *et al.*,[39] using multivariate analysis, indicated that male sex, age > 39 years, DM, and previous dialysis time were prognostic factors of higher risk for mortality in KT recipients. Oniscu *et al.*[40] conducted a study in Scotland with 1095 patients and demonstrated that the relative risk of death adjusted to the comorbidities of all patients, aged 18 to > 65 years, was significantly higher in patients > 50 years of age than in younger patients. In our study, the patient age was > 40 years in 45% of the deaths due to infection and in 80% of the cardiovascular-related deaths.

According to the 2008 annual report from the United Network for Organs Sharing (UNOS)41 that was based on the relative data of kidney transplants in the United States between 1997 and 2007, the respective survival rates of patients at 1, 3, 5, and 10 years post-transplant were 98.9%, 96.4%, 92.9%, and 79.3% from a live donor; the respective rates in the case of deceased donors were 96.4%, 91.3%, 84.7%, and 62.7%. According to the 2011 Brazilian Transplant Record of the ABTO based on the record started on January 1, 2010, the 1-year survival rate for patients with live donors is 97%, and this rate is 91% for those with a deceased donor.[28]

The Kidney and Hypertension Hospital of the UNIFESP, which has developed the largest KT program in the world, showed respective 1- and 2-year patient survival rates of 97.5% and 95.3% with live donors and of 98.7% and 88.3% with deceased donors for all 2,364 kidney transplants performed between January 2003 and December 2006.[18] In 2011, Ferreira *et al.*[42] of the Kidney Transplant Center of the University of São Paulo, reported survival rates

after 1, 5, and 10 years for next-of-kin live donors of 96%, 91.6%, and 89.1%, respectively; for unrelated live donors these rates were 95.3%, 92.4%, and 84.7%, respectively.

In Botucatu, São Paulo, in a series with 108 patients, the respective survival rates of the patients at 1, 3, and 5 years were 92.4%, 92.4%, and 89.2% with live donors, and 82.6%, 77.8%, and 77.8% with deceased donors; these differences were not statistically significant ($p$ = 0.09). In that same study, the main causes of death were cardiovascular factors (38.5%) and infection (38.5%), and most deaths (84.6%) occurred in the first year of follow-up,[43] similar to our results.

The survival rates recorded in the KT center of the HUUFMA were 97.8%, 94.1%, and 92.9% for 1, 3, and 5 years, respectively, with a live donor, and 95.6% and 95.6% with a deceased donor for 1 and 3 years, respectively. At our institution, the KT program started in March of 2000 with only the modality of living donors. In 2005, the modality with deceased donors was initiated, which is why the 5-year survival rates were not reported for this segment of the cohort.

Some studies regarding patient survival after KT in the northeast region of Brazil were negative, thus it was impossible to compare our studies on a regional level, particularly because of characteristics that are peculiar and common to the states in the northeast in relation to the states in the south-southeast axis. We observed that many northeastern states are prominent nationwide in terms of transplantation activity, particularly in the management of the donation-transplant process, which has been reflected in the numbers of the ABTO records.

In this study, only age > 40 years and surgical complications were factors associated with decreased survival of KT recipients.

However, the study is limited due to its design, which did not enable the establishment of a significant link between mortality in KT recipients and other factors such as DM, coronary artery disease, LVH, anemia, dyslipidemia, obesity, chronic infections by hepatitis B and C viruses, and dialysis time, which have been reported as significant factors of mortality in this patient population in the literature. Therefore, further studies are required in this regard.

Infectious complications constituted the main cause of death in this study. More effective clinical strategies of control, both for the early detection of infection as well as for treatment, will benefit KT recipients and decrease mortality.

Finally, it was possible to conclude that the survival rates of KT recipients in Maranhão were similar to those found in other national and international studies, and that recipients aged > 40 years and with surgical complications showed a higher mortality risk. These findings suggest that clinical measures that are directed at these patients should be adopted while considering the short- and long-term qualitative improvement of KTs in Maranhão.

## References


1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation and recipients of a first cadaver transplant. N Engl J Med 1999;341:1725-30.
2. Howard RJ, Patton PR, Reed AI, Hemming AW, Van der Werf WJ, Pfaff WW, et al. The changing causes of graft loss and death after kidney transplantation. Transplantation 2002;73:1923-8.
3. Salermo MP, Zichichi E, Rossi E, Favi E, Gargiulo A, Spagnoletti G, et al. Evolution of causes of mortality in renal transplantation in the last 10 years. Transplant Proc 2010;42:1077-9.
4. Fellström B, Jardine AG, Soveri I, Cole E, Neumayer HH, Maes B, et al. Renal dysfunction is a strong and independent risk factor for mortality and cardiovascular complications in renal transplantation. Am J Transplant 2005;5:1986-91.
5. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation 2006;82:603-11.
6. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007;357:2601-14.
7. Colombo Arnaldo L, Silva Vinícius P. Infecções fúngicas em pacientes submetidos a transplante renal. Prática Hospitalar 2005;42. Disponível em: http://www.praticahospitalar.com.br/pratica 42/pgs/materia 16-42.html
8. Vicente IR, Gutiérrez- Dalmau A, Campistol JM. Immunosuppressive drugs and malignancies. In: Stallone G,Grinyó J, editors. Malignancies in solid organ transplant recipients. Barcelona: Permanyer Publications; 2008. p.15-33.
9. V Diretrizes Brasileiras de Hipertensão Arterial (2006). In: Andrade Jadelson (coordenação). Diretrizes da Sociedade Brasileira de Cardiologia. 2ª ed. São Paulo: Omnifarma; 2009. p.227-45.
10. Imoagene-Oyedeji AE, Rosas SE, Doyle AM, Goral S, Bloom RD. Posttransplantation anemia at 12 months in kidney recipients treated with mycophenolate mofetil: risk factors and implications for mortality. J Am Soc Nephrol. 2006;17(11):3240-7.

11. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
12. Pittman JR, Bross MH. Diagnosis and management of gout. Am Fam Physician 1999;59:1799-806.
13. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998;6:51S-209S.
14. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's, guidelines and standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
15. Gaston RS. Current and evolving immunosuppressive regimens in kidney transplantation. Am J Kidney Dis 2006;47:S3-21.
16. Hosmer Jr DW, Lemeshow S. Applied survival analysis: regression modeling of time to event data. New York: John Wiley & Sons;1998.
17. Ingsathit A, Avihingsanon Y, Rattanasiri S, Premasathian N, Pongskul C, Jittikanont S, et al. Different etiologies of graft loss and death in Asian kidney transplant recipients: a report from Thai Transplant Registry. Transplant Proc 2010;42:4014-6.
18. Harada KM, Sampaio ELM, Freitas TVS, Felipe CR, Park SI, Machado PGP, et al. Fatores de risco associados à perda do enxerto e óbito após o transplante renal. J Bras Nefrol 2008;30:213-20.
19. Sousa SR, Galante NZ, Barbosa DA, Pestana JOM. Incidência e fatores de risco para complicações infecciosas no primeiro ano após o transplante renal. J Bras Nefrol 2010;32:77-84.
20. De Marco FVC, Higa A, Silva RG, Pestana JOM, Santos OFP. Septic shock etiology in kidney transplant recipients. Crit Care 2002;6. Disponível em: http://ccforum.com/supplements/6/S1
21. Linares L, Cofán F, Cervera C, Ricart MJ, Oppenheimer F, Campistol JM, et al. Infection-related mortality in a large cohort of renal transplant recipients. Transplant Proc 2007;39:2225-7.
22. Varma PP, Hooda AK, Sinha T, Chopra GS, Karan SC, Sethi GS, et al. Renal transplantation - an experience of 500 patients. MJAFI 2007;63:107-11.
23. Vinod PB, Sharma RK. Opportunistic infections (non-cytomegalovirus) in live related renal transplant recipients. Indian J Urol 2009;25:161-8.
24. Cosio FG, Alamir A, Yim S, Pesavento TE, Falkenhain ME, Henry ML, et al. Patient survival after renal transplantation: I. The Impact of dialysis pre-transplant. Kidney Int 1998;53:767-72.
25. Goldfarb-Rumyantzev A, Hurdle JF, Scandling J, Wang Z, Baird B, Barenbaum L, et al. Duration of end-stage renal disease and kidney transplant outcome. Nephrol Dial Transplant 2005;20:167-75.
26. Arend SM, Mallat MJ, Westendorp RJ, van der Woude FJ, van Es LA. Patient survival after renal transplantation; more than 25 years follow-up. Nephrol Dial Transplant 1997;12:1672-9.
27. Kimura T, Ishikawa N, Fujiwara T, Sakuma Y, Nukui A, Yashi M, et al. Kidney transplantation in patients with long-term (more than 15 years) prior dialysis therapy. Transplant Proc 2012;44:75-6.
28. Registro Brasileiro de Transplantes-RBT 2011. Associação Brasileira de Transplante de Órgãos; ano XVII- nº 4. Disponível em: http://www.abto.org.br/abtov02/portugues/rbt
29. Medina-Pestana JO, Galante NZ, Tedesco-Silva Jr H, Harada KM, Garcia VD, Abbud-Filho M, et al. O contexto do transplante renal no Brasil e sua disparidade geográfica. J Bras Nefrol 2011;33:472-84.
30. Registro Brasileiro de Transplantes-RBT 2008. Associação Brasileira de Transplante de Órgãos; ano XIV- nº 2. Disponível em: http://www.abto.org.br/abtov02/portugues/rbt
31. Registro Brasileiro de Transplantes-RBT 2009. Associação Brasileira de Transplante de Órgãos; ano XV- nº 4. Disponível em: http://www.abto.org.br/abtov02/portugues/rbt
32. Meier-Kriesche H, Arndorfer JA, Kaplan B. Association of antibody induction with short-and long-term cause-specific mortality in renal transplant recipients. J Am Soc Nephrol 2002;13:769-72.
33. Shirali AC, Bia MJ. Management of cardiovascular disease in renal transplant recipients. Clin J Am Soc Nephrol 2008;3:491-504.
34. Marcén R. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. Drugs 2009;69:2227-43.
35. Orsenigo E, Casiraghi T, Socci C, Zuber V, Caldara R, Secchi A, et al. Impact of recipient and donor ages on patient and graft survival after kidney transplantation. Transplant Proc 2007;39:1830-2.
36. Cosio FG, Hickson LJ, Griffin MD, Stegall MD, Kudva Y. Patient survival and cardiovascular risk after kidney transplantation: the challenge of diabetes. Am J Transplant 2008;8:593-9.
37. Soveri I, Holdaas H, Jardine A, Gimpelewicz C, Staffler B, Fellström B. Renal transplant dysfunction - importance quantified in comparison with traditional risk factors for cardiovascular disease and mortality. Nephrol Dial Transplant 2006;21:2282-9.
38. Moreso F, Ortega F, Mendiluce A. Recipient age as a determinant factor of patient and graft survival. Nephrol Dial Transplant 2004;19:iii16-20.

39. Gentil MA, Pérez-Valdivia MA, Muñoz-Terol JM, Borrego J, Mazuecos A, Osuna A, et al. Are we still making progress in patient survival after kidney transplantation? Results of a regional registry. Transplant Proc 2009;41:2085-8.
40. Oniscu GC, Brown H, Forsythe JL. How old is old for transplantation? Am J Transplant 2004;4:2067-74.
41. OPTN/SRTR 2008 Annual Report. Disponível em: http://www.ustransplant.org/publications/publications.aspx?term=annual report&t=both
42. Ferreira GF, Marques IDB, Park CHL, Machado DJB, Lemos FBC, Paula FJ, et al. Análise de 10 anos de seguimento de transplantes renais com doador vivo não aparentado. J Bras Nefrol 2011;33:345-350.
43. Carvalho MFC. Transplante renal: fatores clínicos associados à piora tardia da função do enxerto - experiência de 10 anos na faculdade de medicina de Botucatu [dissertação]. Botucatu: Universidade Estadual Paulista; 2000.