

# Risk Factors of Graft Survival After Diagnosis of Post-kidney Transplant Malignancy: Using Cox Proportional Hazard Model

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## Abstract

**Background:** All recipients of kidney transplantation, especially those with posttransplant malignancy, are at risk of long-term graft failure.

**Objectives:** The purpose of our study was to evaluate the risk factors associated with graft survival after diagnosis of malignancy.

**Patients and Methods:** To reach this purpose, we conducted a historical cohort study in Iran and 266 cases with posttransplant malignancy were followed up from diagnosis of malignancy until long-term graft loss or the date of last visit. These patients were taken as a census from 16 Transplant Centers in Iran during 22 years follow-up period since October 1984 to December 2008. A Cox proportional hazards model was performed to determine the important independent predictors of graft survival after malignancy.

**Results:** At the end of the study, long-term graft failure was seen in 27 (10.2%) cases. One-year and 2-year graft survival after diagnosis of cancer were 93.6% and 91.7%, respectively. The univariate analysis showed that the incidence of chronic graft loss was significantly higher in male patients with solid cancers, withdrawal of immunosuppressant regimen, no response to treatment, and tumor metastasis. In continuation, the Cox model indicated that the significant risk factors associated with graft survival were type of cancer ( $P < 0.0001$ ), response to treatment ( $P < 0.0001$ , HR = 0.14, 95% CI: 0.06 - 0.32), metastasis ( $P < 0.0001$ , HR = 5.68, 95% CI: 2.24 - 14.42), and treatment modality ( $P = 0.0001$ ).

**Conclusions:** By controlling the modifiable risk factors and modality of treatment in our study, physicians can reach more effective treatment.

**Keywords:** Neoplasms, Kidney Transplant, Proportional Hazards Model

## 1. Background

Malignancy is one of the most common complications after kidney transplant. It is the second cause of death in kidney transplant recipients (1). The overall incidence of malignancy after kidney transplant has been reported to be 3 to 5 times higher than general population (2, 3).

An increased incidence of malignant tumors in transplant recipients was recognized as early as in the 1970s, and was ascribed to the administration of immunosuppressive medications (4, 5).

Incidence and type of cancer after kidney transplant vary among centers, countries, and time periods (6). According to the Cincinnati Transplant Tumor Registry and other reports, the most frequent types of tumors are posttransplant lymphoproliferative disorder (PTLD) and squamous cell carcinoma (lip, cervix, vulva, skin) (7, 8).

All recipients, especially recipients with posttransplant malignancy, are at risk of long-term graft loss. One-year survival of graft after kidney transplant in Iran is 94.7% (9). Also 1-year graft

survival in recipients from living unrelated donors (LURD) and living related donors (LRD) are 85.6% and 97.4%, respectively (10).

Many studies have investigated the factors related to graft survival in the population of recipients. For example, there are several factors that predict long-term graft loss after transplantation. Recipient factors included age, weight, gender, BMI, race, cause of renal failure, induction therapy, presence of surgical complications, CVD (cardiovascular disease) complications, diabetes, depression, infections, same side transplanted kidney, known primary disease, use of mycophenolate mofetil, sirolimus and/or calcineurin inhibitors, acute rejection episodes, any treated rejection episode, delayed graft function, Black race, recurrence of glomerular disease, and death with a functioning graft. Donor factors included BMI, creatinine, HLA mismatch, age, gender, race, donor/recipient relationship, and type of operation procedure (open vs. laparoscopic). Also donor factors affecting long-term posttransplant graft survival

included age, race, sex, cause of death, cold ischemia time, HLA matching, organs from expanded-criteria donors, and cytomegalovirus (CMV) status (10-16).

But, few studies have evaluated graft survival in recipients with posttransplant malignancy. In some of the studies, investigators concluded that the presence of malignancy in some of patients is the main cause of death and graft failure (17). Other studies suggested that medical complications such as cardiovascular disease (CVD), infection, and malignancy were the most common cause of graft loss (18-20).

## 2. Objectives

Because of the occurrence of malignancy in this population, graft survival and its associated factors are important. So we designed this study to investigate the risk factors of kidney graft survival after diagnosis of posttransplant malignancy.

## 3. Patients and Methods

We evaluated population of recipients that suffered from malignancy collected by Behzad Einollahi et al. They conducted a multicenter study on 12525 kidney recipients in Iran during 24 years follow-up period since October 1984 to December 2008. They collected 266 (2%) biopsy-proven malignancy cases of 26 different types from 16 Transplant Centers in Iran (21). Sixteen Transplant Centers were located in cities of Tehran, Ahvaz, Zanjan, Mashhad, Babol, Isfahan, Kermanshah, Kerman, Rasht, Urmia, Tabriz, and Shiraz. The patients were taken as a census from 16 Transplant Centers in Iran. In this historical cohort study, 266 cases with post-transplant malignancy were followed up from diagnosis of malignancy until long-term graft loss or the date of their last visit. Patients with other organ transplants, history of previous malignancy and transplantation from deceased donors with the history of malignancy were excluded from the study. This study was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences (code: 35, date: March 10, 2014).

The purpose of our study was to evaluate risk factors associated with survival of the graft. To this effect, by using the univariate analysis, at first we compared incidence of graft loss at the level of covariates by Chi-square test, Fisher exact test, and t test. The significance level was set at  $P < 0.05$ . Quantitative and qualitative variables were expressed as mean  $\pm$  SD and percentage, respectively. In continuation, a Cox proportional hazards model was performed by SPSS version 20 to determine the important independent predictors of graft survival after malignancy. The proportionality assumption for this model was checked by log-log curves.

As this study was a historical cohort one, data were collected from previous medical records in the transplant centers. When the missing clinical variables were high, they were excluded from analysis.

The candidate predictors for including in the model were gender, age, type of cancer, transplantation time until diagnosis (month), age at the time of diagnosis, ALG/ATG, treatment modality, response to treatment, metastasis, CMV

infection after cancer, and immunosuppressive regimen.

The definitions of some covariates are:

Type of the cancer: Patients with tumor were categorized into 5 groups according to their type of neoplasm: Non-KS, KS, PTLD, GU and RS tumors, and solid tumors. Non-Kaposi's sarcoma tumors (non-KS) included SCC (squamous cell carcinoma), BCC (basal cell carcinoma), and melanoma. Tumors of breast, ovary and uterine in females, prostate and seminoma in males and renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) of bladder in both gender were considered as genitourinary and reproductive system (GU and RS) neoplasms. The term of solid tumors was used for all malignancies except skin tumors, PTLD (posttransplant lymphoproliferative disorder) and GU and RS cancers.

Treatment modality: Treatment modalities were considered according to the type of cancer, staging of disease, and involved organs. Management included a combination of reduction, withdrawal, or changing of the immunosuppressive agents, chemotherapy, radiotherapy, hormone therapy, and surgical resection.

(ATG/ALG): Monoclonal antibody (ATG/ALG) can be required for induction therapy and acute steroid-resistant rejection episodes during the first 3 months following kidney transplantation. Induction therapy with ATG/ALG was used for highly sensitized patients, those receiving kidneys from deceased donors with delayed graft function, patients with poorly matching living donors, and those with the second or more transplants. None of the patients took OKT3.

Immunosuppression protocols: The immunosuppressive therapy was based on cyclosporine/sirolimus, mycophenolate mofetil (MMF)/azathioprine (AZA), and steroids. Before 2000, patients received dual maintenance immunosuppression with prednisone and cyclosporine/AZA or triple therapy with cyclosporine, prednisone, and AZA. Afterwards, the majority of patients received cyclosporine, prednisone, and MMF as well.

## 4. Results

The patients with malignancy were followed up after diagnosis of cancer for a median time of 22 months (1 - 168 months). The mean age at the time of diagnosis of cancer was  $50.8 \pm 13.2$  years (range 15.5 - 82.0 years) and the mean interval between transplant and diagnosis of malignancy was  $51.08 \pm 48.6$  months. A total of 180 (67.7%) of recipients were male. The long-term graft loss was seen in 27 (10.2%) cases. Figure 1 shows graft survival functions for this data. According to Figure 1, the 1-year and 2-year graft survival after diagnosis of cancer were 93.6% and 91.7%, respectively.

Table 1 shows the incidence of chronic graft loss in patients with posttransplant malignancies according to covariates. According to Table 1, incidence of chronic graft loss was significantly higher in male patients with solid cancers, withdrawal of immunosuppressant, no response to treatment, and metastasis of tumor.

Furthermore, Table 2 shows the hazard ratios (HR) and standard errors of significant risk factors of graft survival

after malignancy by using Cox proportional model. This model indicated that the significant risk factors associated with graft survival are type of the cancer ( $P < 0.0001$ ), response to treatment ( $P < 0.0001$ ,  $HR=0.14$ ), metastasis ( $P < 0.0001$ ,  $HR = 5.68$ ), and treatment modality ( $P = 0.0001$ ). The parallel lines of log-log curves for the level of these variables approved their proportionality assumption. Hazards of graft loss for PTLD and GU and RS cancers were similar to KS cancer. But the hazard of graft loss was higher in solid cancer cases and lower in non-KS cancer cases, compared to KS cancer cases. Hazard of long-term graft loss in unmodified treatment modality was similar to that of patients with withdrawal of immunosuppression (i.e. without group), while change of immunosuppressive drugs or their dose decreases hazards of long-term graft loss versus withdrawal of immunosuppressant. Response to treatment decreased the hazards of graft loss but metastasis of tumor increased this hazard in patients with malignancy (Table 2).

Figure 2 shows graft survival functions for types of cancer. According to Figure 2, the patients with non-KS cancer had

the lowest hazard of graft loss after diagnosis of cancer (or highest graft survival) and patients with solid cancer had the highest hazard of graft loss (or lowest graft survival).

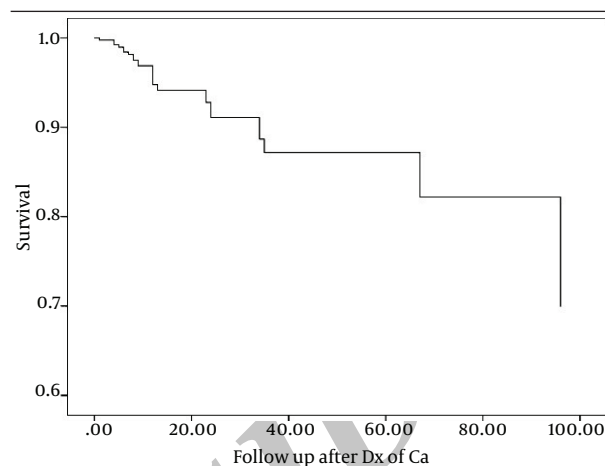


Figure 1. Graft Survival Function for Cox Model

Table 1. Long-term Graft Survival in Patient With Posttransplant Malignancies<sup>a</sup>

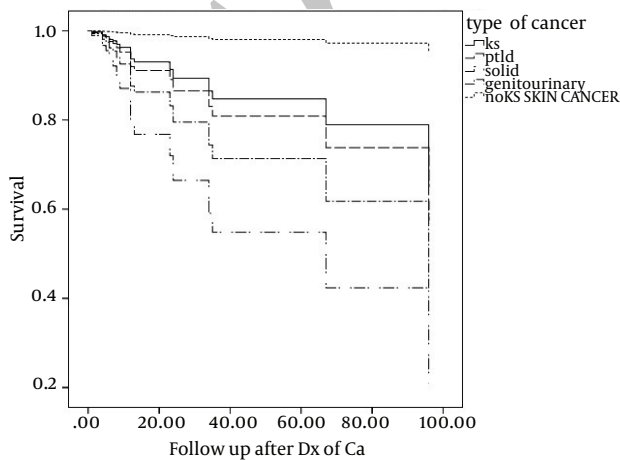
Variables	Total Number	Long-term Graft Loss Number, %		P Value
		No	Yes	
<b>Gender</b>				0.040
Male	180	157 (87.2)	23 (12.8)	
Female	86	82 (95.3)	4 (4.7)	
<b>Cancer</b>				0.055
KS	84	74 (88.1)	10 (11.9)	
Non-KS	57	56 (98.2)	1 (1.8)	
PTLD	72	65 (90.3)	7 (9.7)	
GU & RS	25	21 (84.0)	4 (16.0)	
Solid	28	23 (82.1)	5 (17.9)	
<b>ALG/ATG</b>				0.110
No	183	168 (91.8)	15 (8.2)	
Yes	36	30 (83.3)	6 (16.7)	
<b>Treatment modality</b>				0.0001
Without	80	58 (72.5)	22 (27.5)	
Decrease	74	71 (95.9)	3 (4.1)	
Change	29	28 (96.6)	1 (3.4)	
Unmodified	25	24 (96)	1 (4)	
<b>Response to treat</b>				0.02
No	74	60 (81.1)	14 (18.9)	
Yes	162	149 (92)	13 (8.0)	
<b>Metastasis</b>				0.002
No	156	147 (94.2)	9 (5.8)	
Yes	50	40 (80)	10 (20.0)	
<b>CMV infection after cancer</b>				0.801
No	43	37 (86)	6 (14.0)	
Yes	12	10 (83.3)	2 (16.7)	
<b>Immunosuppressive regimen</b>				0.081
MMF	96	91 (94.8)	5 (5.2)	
AZA	152	134 (88.2)	18 (11.8)	
<b>Age, y</b>	46.2 ± 12.9	46.5 ± 13.07	43.3 ± 11.4	0.230
<b>Transplantation until diagnosis (month)</b>	51.08 ± 48.6	51.3 ± 47.2	48.6 ± 60.2	0.790
<b>Age at the time of diagnosis, y</b>	50.8 ± 13.2	51.2 ± 13.1	47.6 ± 13.8	0.210

<sup>a</sup>Abbreviations: ALG/ATG, Antilymphocyte/antithymocyte globulin; AZA, Azathioprine; CMV, Cytomegalovirus; GU and RS, Genitourinary and Reproductive system; KS, Kaposi's sarcoma; MMF, Mycophenolate mofetil; Non-KS, Non Kaposi's sarcoma; PTLD, Posttransplant lymphoproliferative disorder.

**Table 2.** Factors Associated With Long-term Graft Survival in Patients with Post-transplant Malignancies in Cox Model<sup>a</sup>

Variables	Hazard Ratio	95% CI		P Value
		Lower	Upper	
<b>Cancer</b>				
KS	Base Category			
Non-KS	0.11	0.013	0.93	0.042
PTLD	1.28	0.482	3.41	0.610
GU and RS	2.03	0.62	6.65	0.240
Solid	3.62	1.18	11.04	0.020
<b>Treatment modality</b>				
Without	Base Category			
Decrease	0.122	0.04	0.37	0.001
Change	0.12	0.01	0.96	0.040
Unmodified	0.16	0.02	1.14	0.070
<b>Response to treatment</b>				< 0.0001
No	Base Category			
Yes	0.14	0.06	0.32	
<b>Metastasis</b>				< 0.0001
No	Base Category			
Yes	5.68	2.24	14.42	

<sup>a</sup>Abbreviations: ALG/ATG, Antilymphocyte/Antithymocyte globulin; GU and RS, Genitourinary and Reproductive system; KS, Kaposi's sarcoma; Non-KS, Non Kaposi's sarcoma; PTLD, Posttransplant lymphoproliferative disorder.



**Figure 2.** Graft Survival Function for Cox Model According to the Types of Cancer

### 5. Discussion

Our study aimed to evaluate the risk factors of graft survival in the recipients with post-transplant malignancy. Evaluating risk factors that change hazards of long-term graft loss, especially in recipients diagnosed with cancer, is an important research goal. For this study, we used data of multicenter study that was conducted by Einollahi et al. They concluded that the skin (52.9%) and PTLD (27%) cancer were the most frequently observed malignancy after renal cancer (21).

Our study showed that the long-term graft loss was seen in 27 (10.2%) cases. The graft 1-year survival after diagnosis of cancer was 93.6%. Other studies in Iran also reported 1-year survival of graft after kidney transplant as 94.7% (9), or 85.6% and 97.4% (10). These 2 survival rate have different definitions, 93.6% is the survival rate after diagnosis of cancer but 94.7% is the survival rate after transplantation. Thus these 2 rates are not comparable.

Errasti et al. concluded in their study that the presence of malignancy in some patients is the main cause of graft fail-



ure (17). In this context, our results indicated that the type of cancer has a significant relationship with graft survival after diagnosis of cancer and solid cancers had the highest hazards to long-term graft loss. Also Dantal and Pohanka found that solid organ cancers, although less common, are associated with a far worse prognosis in renal transplant recipients (22) that perhaps justified this result.

In some studies, it has been concluded that improvements in immunosuppressive regimens and general care of the kidney transplant recipient have led to significantly enhanced graft survival (23, 24). The results of our study confirmed these findings. Our study showed that decreasing dose or changing of immunosuppressive drugs decreases the hazard of long-term graft loss or prolongs the graft survival after cancer. But Vanhove et al. showed that MMF dose reductions in  $\geq 50\%$  did not compromise graft survival (25).

Also we showed that failure to treatment and metastasis of tumor increase the hazard of long-term graft loss. However, there was no relationship between gender, age, CMV infection, and type of immunosuppressive regimen with survival of graft after cancer. The effects of these factors are different in other studies. Unlike our study, Braun et al. (11) and Rao et al. (16) showed in their studies that cytomegalovirus (CMV) infection and other infections were independent risk factors of recipients for graft loss (11, 16). Also Briganti et al. (26) and Wigmore et al. (27) showed that older age of the recipient was a predictive factor for reduction of 12-month graft survival. However, similar to our study, Saudan et al. (28) concluded that graft survival was not different between the two recipient age groups. In addition, Kolonko et al. indicated that risk for graft loss was significantly higher in females (29).

As this study was retrospective and data have been collected from previous medical records and all contributing factors were not accessible, some missing data and probability of evaluation of only some especial risk factors were two limitations of this study.

Results and findings of this study can guide nephrologists in general care of the kidney transplant recipients. By controlling the modifiable risk factors and the modality of treatment, physicians can provide more effective treatment. For example, in the recipients with solid cancer, no response to treatment, or metastasis of tumor who are at high risk of chronic graft loss, nephrologists can focus on the change of immunosuppressive drugs or decrease their dose to prolong graft survival after diagnosis of cancer.

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## Footnotes

**Authors' Contributions:** Study design: Behzad Einollahi and Zohreh Rostami; Statistical analysis and interpretation of data: Mahmoud Salehi and Mohammad Reza Eshraghian Drafting of the manuscript: Mahmoud Salehi, Zohreh Rostami, Jamile Mohammadi, and Ali Reza Mehrazmai.

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