Impact of Pre-Transplant Malignancy on Outcomes After Kidney Transplantation: United Network for Organ Sharing Database Analysis

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BACKGROUND: Kidney transplant recipients with a history of a pre-transplant malignancy (pre-TM) have an increased risk of post-transplant malignancies (post-TM) and suspected inferior long-term outcomes. No large database studies have examined modern day trends and outcomes in this patient population compared with those without a pre-TM.

STUDY DESIGN: The United Network for Organ Sharing (UNOS) database was queried for primary adult kidney transplant recipients with pre-TM. Outcomes were compared in patients with and without pre-TM from 2004 to 2016 using multivariable Cox proportional hazard analyses (n = 170,684).

RESULTS: The rate of kidney transplants in patients with pre-TM increased from <1% of all kidney transplants in 1994 (n = 77) to 8.3% in 2016 (n = 1,329). Pre-TM was associated with development of post-TM (hazard ratio [HR] 1.77 CI 1.68, 1.86), all cause (HR 1.22 CI 1.18, 1.27), and death-censored graft failure (HR 1.08 CI 1.02, 1.15) between 2004 and 2016. The 5-year all cause graft failure rate was 28% for pre-TM patients and 22% for non-pre-TM patients. Pre-TM was associated with decreased patient survival (5-year 80% vs 88% and HR 1.23 CI 1.18, 1.28). Of the deceased, more pre-TM patients died of malignancy (19% vs 11%).

CONCLUSIONS: Increasing numbers of patients with pre-TM are undergoing kidney transplantation. This analysis indicates that patients with pre-TM are at increased risk of post-TM, graft loss, and decreased overall survival. The study's limitations highlight the need for collaborative database development between transplant and cancer registries to better define the interrelationship between a pre-TM and cancer survivorship vs freedom from prolonged dialysis. (J Am Coll Surg 2019;229:568−579. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Improvements in the multidisciplinary care of patients with end-stage renal disease (ESRD) have led to an increase in long-term survival and an increase in the number of these patients with associated malignancies.[1] In addition, as the US population ages[2] and cancer treatments improve with decreased overall cancer mortality

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Abbreviations and Acronyms

ACGF	= all cause graft failure
DCGF	= death-censored graft failure
ECD	= extended criteria donor
ESRD	= end-stage renal disease
HR	= hazard ratio
NMSC	= nonmelanoma skin cancer
OPTN	= Organ Procurement and Transplantation Network
post-TM	= post-transplant malignancy
pre-TM	= pre-transplant malignancy
UNOS	= United Network for Organ Sharing

rates,[3] more individuals, many with a history of malignancy, are developing renal disease.[4,5] Therefore, there is a growing population of patients who have both ESRD and a previous cancer diagnosis.

The definitive treatment for ESRD is kidney transplantation. However, the requirement for immunosuppression after transplant is a major risk factor contributing to the increased risk of post-transplant malignancy (post-TM) compared with that in the general population.[6] Despite this risk, more older patients are now eligible for kidney transplant due to better-targeted immunosuppression regimens, improved anti-infective prophylaxis, and technical advancements with organ recovery and transplantation.[7-11] Increasingly, kidney transplantation is being performed in patients greater than 65 years of age, with dramatic improvements in both patient and graft survival.[9] The increased availability of extended criteria donor (ECD) kidneys, organs that previously would have been discarded due to poorer quality or donor risk factors, have also expanded the available donor pool and made transplantation available to more patients who may not have been candidates for a non-ECD kidney due to comorbidities and increasing age.[10]

Kidney transplantation in patients with a history of previous malignancy has historically been limited because of concerns of increased malignancy after transplantation.[12,13] Current US guidelines generally recommend a 2- to 5-year tumor-free waiting period before transplantation for most malignancies, unless the malignancy is considered cured (for example, basal cell or squamous cell carcinoma) at the time of transplant, in which case no waiting period is required.[14] It is important to note that there is little consensus in guidelines for transplantation after a diagnosis of malignancy, with wide variation in waiting periods around the globe.[15] Previous studies have demonstrated a wide range in the risk of cancer recurrence after transplantation, from 1% to 25%, depending on the study type, era in which it was performed, and type of malignancy.[16-19] Kidney transplant recipients with a history of pre-transplant malignancy (pre-TM) have previously been shown to have a 2- to 3-fold higher risk of dying from cancer compared with transplant recipients without pre-TM.[19-21] The majority of these studies were performed before ECD kidney availability, in younger patients with fewer comorbidities, or were limited by small numbers of pre-TM kidney transplant recipients.[16,17,19-21] Based on the overall aging population, the changing landscape of ESRD, and the increased demand for kidney transplantation, we hypothesized that an increasing number of individuals with pre-TM were undergoing transplantation. The objectives of this study were to determine the frequency of kidney transplantation in patients with pre-TM over a 22-year period, and evaluate post-transplant outcomes of these transplant recipients by using a large national database of transplant recipients.

METHODS

Study population

The United Network for Organ Sharing (UNOS) requires all solid organ transplants occurring in the United States to be reported to the Organ Procurement and Transplantation Network (OPTN). We queried the UNOS/OPTN database for all adult primary kidney transplant recipients who underwent transplantation between 1994 and 2016 (n = 331,329). Patients who had received multiorgan transplants (n = 40,190) were excluded from analysis. We chose 1994 for the start date because it was in that year that UNOS started collecting data on pre-TM from patients on the waiting list for kidney transplants. Due to concerns about the quality of data and missing-ness of several covariates of interest, only patients who underwent transplantation from 2004 to 2016 were included in multivariable analysis (n = 184,955). Patients whose pre-TM status was unknown (n = 14,271) were excluded from the analysis. Long-term outcomes from this study are based on OPTN data as of September 8, 2017. This retrospective study was approved by the University of Wisconsin Institutional Review Board.

Analysis and statistics

The primary outcomes of this study were development of post-TM, all cause graft failure (ACGF), death-censored graft failure (DCGF), and overall patient survival. The OPTN definition of graft failure includes the death of any transplant recipient, regardless of cause of death or functional status of graft.[22] In order to evaluate the impact of pre-TM on graft function we elected to evaluate DCGF, where only patients with nonfunctioning

Table 1. Demographic of Patient Study Population

Variable	No pre-TM (n = 158,993)	Pre-TM (n = 11,691)
Median follow-up, months (range)	48 (0–165)	39 (0–159)
Female, n (%)	61,931 (39)	4,153 (36)
Age, n (%)		
18–39 y	12,622 (8)	182 (2)
40–64 y	119,445 (75)	6,567 (56)
≥65 y	26,926 (17)	4,942 (42)
Race, n (%)		
White	77,425 (49)	8,345 (71)
Black	42,903 (27)	2,104 (18)
Hispanic	25,699 (16)	769 (7)
Other	12,966 (8)	473 (4)
Transplant indication, n (%)		
Auto/inflam	14,960 (9)	621 (5)
Diabetes	42,435 (27)	2,549 (22)
Cancer	0 (0)	637 (5)
HTN	36,045 (23)	2,378 (20)
Other	65,553 (41)	5,506 (47)
Dialysis prior, n (%)	128,671 (81)	8,976 (77)
Deceased donor, n (%)	105,877 (67)	7,425 (64)
Induction agent, n (%)		
None	27,048 (17)	1,876 (16)
ATG	67,200 (42)	4,753 (41)
IL2RB	35,984 (23)	3,201 (27)
CTSD	21,021 (13)	1,311 (11)
2 agents	7,500 (5)	547 (5)
Other	240 (0)	11 (0)
Steroid,* n (%)		
Yes	106,315 (67)	7,452 (64)
No	42,324 (27)	3,459 (30)
Unknown	10,354 (7)	780 (7)
Immunosuppression,* n (%)		
CNI+MMF	137,804 (87)	10,087 (86)
None	4,419 (3)	366 (3)
CNI	8,406 (5)	585 (5)
MMF	8,140 (5)	636 (5)
Other	224 (0)	17 (0)
Date range by year, n (%)		
2004–2007	45,347 (29)	2,289 (20)
2008–2011	48,314 (30)	3,380 (29)
2012–2016	65,332 (41)	6,022 (51)

p Values by chi-square test were <0.01 for all categories.
*Steroid and immunosuppression agent patient was prescribed at time of discharge from initial hospitalization for transplant.
ATG, anti-thymoglobulin; Auto/Inflam, autoimmune or inflammatory renal diseases; CNI, calcineurin inhibitor; CTSD, cell-type specific depletion; HTN, hypertension; IL2RB, interleukin-2 receptor blockade; MMF, mycophenolate mofetil.

allografts are considered to have experienced graft failure, in addition to ACGF. Patients with immediate graft failure (n = 622) or those who died on the day of transplant (n = 96) were excluded from the analyses.

Descriptive statistics were performed on baseline patient characteristics. Recipient age was converted to a categorical variable, as described in Table 1, and differences between groups were evaluated using the chi-

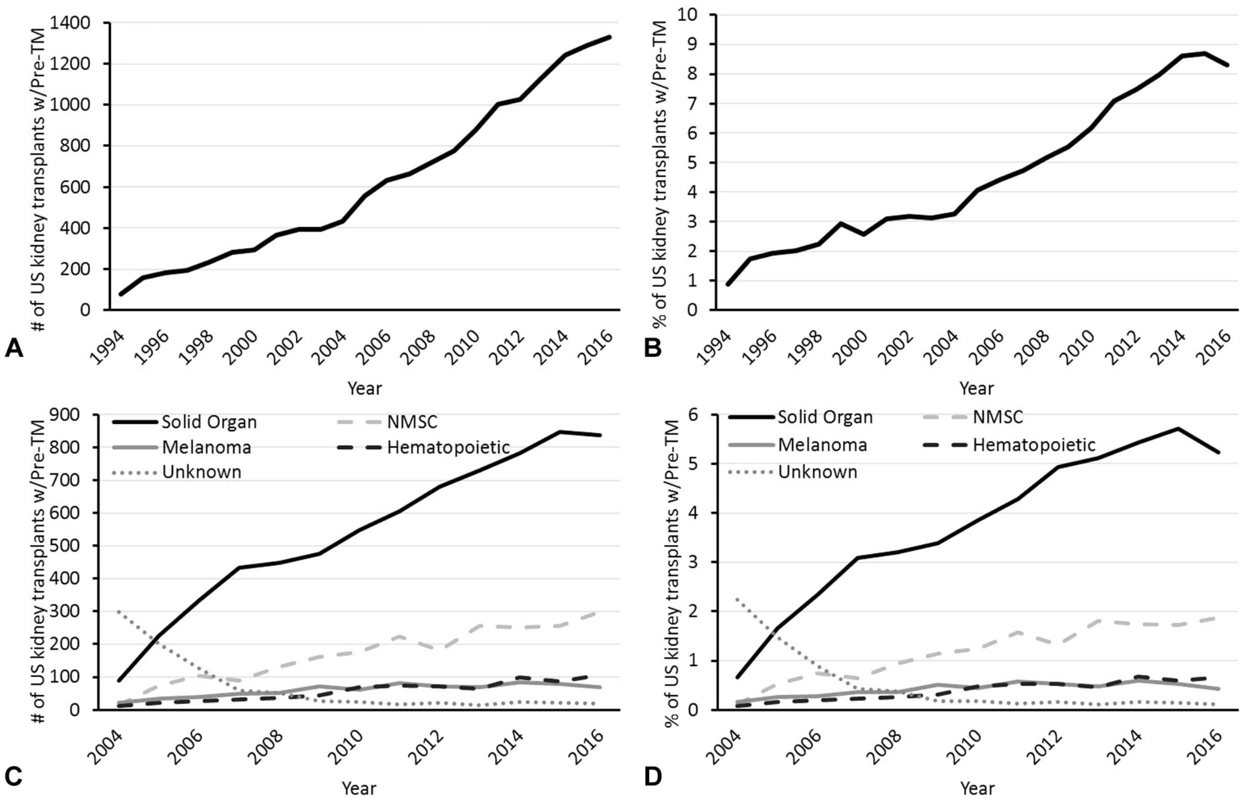

Figure 1. Patients with pre-transplant malignancy (pre-TM) who have received kidney transplants. Patients with any pre-TM who underwent kidney transplantation were identified in the United Network for Organ Sharing (UNOS) database and graphed (A) as total number and (B) percentage of total kidney transplants performed in each year from 1996 through 2016. (C) (D) Pre-TM was stratified by malignancy type for 2004–2016: solid organ, nonmelanoma skin cancer (NMSC), melanoma, hematopoietic cancers, or unknown type, and graphed as in (A) and (B). Before 2004, type of pre-TM was not collected by UNOS, and for this reason, 2004 was chosen as the start date for all subsequent analysis.

square test. Multivariable Cox proportional hazard models were constructed to assess development of post-TM, ACGF, DCGF, and overall patient survival. Kaplan-Meier plots were used to assess the proportionality assumption in Cox models for each outcome of interest. No outcome violated this assumption. To address concerns of competing risk, patients who died before developing graft failure or post-TM malignancy were censored in the Cox models at the time of death.[23]

Covariates were identified based on recipient, donor, and clinical transplant factors available in the UNOS database. Univariate Cox models were constructed for each potential covariate and outcome of interest. The variables found to be statistically significant, defined as $p < 0.05$, were included in multivariable models.

Recipient variables evaluated for post-TM included age, sex, race, education, body mass index (BMI), and whether the patient required dialysis before receiving the kidney transplant. Education was included as a marker of socioeconomic status. We were unable to use duration of dialysis before transplantation as a covariate, as has been previously reported,[24] because this variable was missing for more than 16% of patients reported to have been on dialysis. Transplant-related variables included induction agent, maintenance immunosuppression/steroids prescribed at discharge from initial transplantation hospitalization, and year of transplantation. Induction agents were categorized as: anti-thymoglobulin (ATG), interleukin-2 receptor blockade (IL2RB; including sirolimus, everolimus, daclizumab, and basilizimab), cell-type specific depletion (CTSD; including OKT3, alemtuzumab, and rituximab), and other agents that did not fall into those categories; patients who received 2 induction agents with different mechanisms of action were evaluated separately. We were unable to combine all immunosuppressive agents prescribed at discharge because more than 11,000 patients (7% of cohort) were missing data on whether they were given steroids and included steroids as a separate factor. The remaining maintenance immunosuppression medications were classified into calcineurin

Table 2. Characterization of Pre- and Post-Transplant Malignancies (Pre-TM and Post-TM)

	Pre-TM		Post-TM			
	n = 12,798		No pre-TM, n = 18,611*		Pre-TM, n = 3,016†	
Malignancy	n	%	n	%	n	%
Melanoma	797	6.2	530	2.8	86	2.9
NMSC	2,294	17.9	10,627	57.1	1,998	66.2
Unknown skin	46	0.3	–	–	–	–
Hematopoietic‡	773	6	176	0.9	19	0.6
Breast	983	7.7	625	3.4	60	2.0
Lung	98	0.8	1,233	6.6	157	5.2
Prostate	852	6.7	888	4.8	90	3.0
Colorectal	542	4.2	406	2.2	54	1.8
Renal	1,480	11.5	906	4.9	118	3.9
Other	4,025§	31.4§	3,129‖	16.8‖	424‖	14.1‖
Unknown	908	7.1	91	0.5	10	0.3

*11,493 patients without pre-transplant malignancy (pre-TM) developed post-transplant malignancy (post-TM).
†2,040 patients with pre-TM developed post-transplant malignancy. 228 patients experienced a recurrence of their pre-TM as classified by the United Network for Organ Sharing (UNOS): 17 melanoma, 47 nonmelanoma skin cancer (NMSC), 27 hematopoietic, 110 solid organ/other, and 27 unknown.
‡Includes leukemia, lymphomas, and other myelodysplastic disorders.
§Includes 2,268 unclassified genitourinary cancers as well as cancers that did not fit into the above categories.
‖Includes all known malignancies that did not fit in the above categories.
NMSC, nonmelanoma skin cancer.

inhibitor (CNI; including cyclosporine and tacrolimus), mycophenolate mofetil (MMF), or other agents. To control for potential effects of transplants from different time periods, the years of transplantation evaluated in this study were divided into 3 eras: 2004 to 2007, 2008 to 2011, and 2012 to 2016. In preliminary univariate analysis, all variables listed above, except for BMI (hazard ratio [HR] 1.00 CI 1.00, 1.00 $p = 0.79$), were considered significant and included in the multivariable models.

Recipient-specific variables included in the evaluation of graft failure and patient survival were age, race, diagnosis of diabetes at time of transplant listing, whether the patient required pre-transplant dialysis, and human leukocyte antigen (HLA) mismatch. We did not evaluate panel reactive antibody (PRA) as a variable because it was missing from 28% (n = 47,036) of the cohort. Donor-specific variables included in analysis were age and type of donor (living vs deceased) as well as ECD status. Transplant-specific variables included cold ischemic time, induction agent, steroids and immunosuppression agents prescribed at the time of discharge from the initial transplant hospitalization, transplant era, and whether the patient experienced delayed graft function (DGF). Delayed graft function was defined as requiring dialysis within 1 week of kidney transplant. Rejection episodes were not included because the date of rejection was unknown and therefore could not be analyzed appropriately as a time varying covariate. All variables were significant in univariate analysis and included in the multivariable models. Preliminary multivariable models identified significant collinearity between ECD status and donor type (living or deceased), so ECD status was not included in subsequent models.

Models for all outcomes of interest were established examining all pre-TM together and pre-TM stratified by cancer type. Hazard ratios, confidence intervals, and p values were calculated for each covariate. Descriptive statistics were used to evaluate cause of death. All statistics were performed using STATA 14.0 (StataCorp LP).

RESULTS

The total number (Fig. 1A) and percentage (Fig. 1B) of total US kidney transplants performed in patients with pre-TM have increased from 1994 to 2016. In 1994, 77 patients with pre-TM underwent kidney transplantation, representing 0.9% of total US kidney transplants; by 2016, 1,329 patients with pre-TM received kidney transplants, or 8.3% of the total US kidney transplants. Of patients with pre-TM, patients with a history of solid organ malignancies have received the majority of transplants from 2004 through 2016 (Figs. 1C, 1D). In contrast, transplantation in patients with history of hematopoietic cancers or melanomas has remained constant, at lower levels than those with histories of solid organ or nonmelanoma skin cancer (NMSC).

We identified 11,691 kidney transplant recipients with pre-TM and compared them with 158,993 recipients without pre-TM who received their transplant from 2004 to 2016 (Table 1). Patients with pre-TM were older

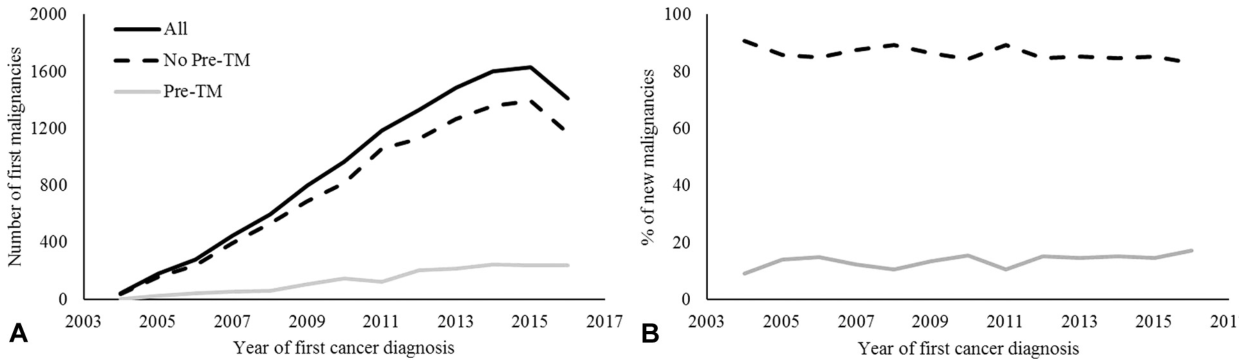

Figure 2. Development of first cancer after kidney transplantation. Patients who developed a first cancer diagnosis after kidney transplantation were identified in the UNOS database and stratified based on whether the patient had pre-transplant malignancy (pre-TM) or not. The data are graphed as (A) the total number of cases diagnosed each year and (B) the percentage of cases diagnosed in each year.

(median age 63 years, range 18 to 89 years vs median age 53 years, range 18 to 96 years), white (71% vs 49%, $p < 0.001$), and fewer had autoimmune/inflammatory diseases or diabetes listed as their transplant indication (5% vs 9%, $p < 0.001$). Six hundred thirty-seven pre-TM patients had cancer listed as their indication for transplant. Fewer patients with pre-TM were on dialysis before transplant (77% vs 81%, $p < 0.001$). The rate of deceased donor transplantation was lower in the pre-TM group (64% vs 67%, $p < 0.001$). More patients with pre-TM received IL2RB induction agents (27% vs 23%, $p < 0.001$), and fewer received steroids at discharge (64% vs 67%, $p < 0.001$).

Pre-TMs (n = 12,798) are summarized in Table 2. Several patients had more than 1 pre-TM, making the total number of pre-TMs higher than the number of pre-TM patients. Approximately 18% of the total cancers were NMSC. Renal cancer was the next most common (11.5%) followed by breast (7.7%), prostate (6.7%), and hematopoietic malignancies (6%). There were 2,268 cancers (17.7% of total cancers) that were labelled as "genitourinary cancers" and included in the "other" category in our analysis; 7% were unknown.

A total of 13,533 individuals in our cohort, 2,040 with pre-TM and 11,493 without pre-TM, developed 21,627 cancers after their kidney transplant (Table 2). The 5-year rate of post-TM in individuals with pre-TM was almost 3 times that of those without pre-TM (21.3% vs 7.3%). Nonmelanoma skin cancer was the most common diagnosis for patients with and without pre-TM (66.2% vs 57.1%), followed by lung cancer (5.2% vs 6.6%). The post-TM of 228 individuals with pre-TM were classified as recurrences of their original pre-TM by UNOS, representing a 2% recurrence rate in pre-TM patients. Of the patients who experienced recurrence, the majority (48%) had solid organ cancers, followed by NMSC (21%), unknown (12%), hematopoietic (12%), and melanomas (7%). Patients with history of pre-TM were 10% to 15% of the total number of malignancies diagnosed in each year (Fig. 2B). In our multivariable analysis, pre-TM was strongly associated with development of a post-TM, with a HR of 1.77 (CI 1.68, 1.86; Table 3). Intriguingly, of patients with known pre-TMs, those with a previous solid organ cancer had the lowest risk of developing a post-transplant malignancy (HR 1.41 CI 1.32, 1.51) when compared with patients without pre-TM. Individuals with NMSC, melanoma, and hematopoietic pre-TMs all had a higher risk of developing post-TM, with HR ranging from 2.02 to 2.62.

Pre-TM was associated with an increased risk of ACGF (HR 1.22 CI 1.18, 1.27; Table 4), with subgroup analysis demonstrating a significant association for all cancer subtypes except melanoma (HR 1.06 CI 0.91, 1.22). The 5-and 10-year rates of ACGF were 26% and 54% for patients with pre-TM, and 22% and 44% for patients without pre-TM, respectively. Pre-TM was associated with an increased risk of DCGF, although the effect was smaller than for ACGF (HR 1.08 CI 1.02, 1.15). However, when individual pre-TM subtypes were evaluated, there was no longer a statistically significant relationship present. The 5- and 10-year rates of DCGF were 10% and 19% for patients with pre-TM and 12% and 26% for patients without pre-TM, respectively.

Pre-TM was independently associated with worse patient survival (HR 1.23 CI 1.18, 1.28; Table 4). The 5- and 10-year overall survival rates were 80% and 55% for patients with pre-TM and 88% and 73% for patients without pre-TM, respectively. Only melanomas were not associated with differences in patient survival; all other pre-TM subtypes were associated with worse survival, ranging from an 18% increased risk for solid organ tumors (HR 1.18 CI 1.11, 1.25) to a doubling of the

Table 3. Multivariable Analysis of Development of First Post-Transplant Malignancy

Variable	Hazard ratio (95% CI)
Previous malignancy	
Any	1.77 (1.68, 1.86)
NMSC	2.53 (2.32, 2.75)
Melanoma	2.02 (1.75, 2.33)
Blood/MDO	2.62 (2.20, 3.12)
Solid organ	1.41 (1.32, 1.51)
Unknown	1.67 (1.45, 1.92)
Age, y	1.05 (1.04, 1.05)
Female	0.73 (0.71, 0.76)
Race	
White	REF
Black	0.41 (0.39, 0.44)
Hispanic	0.39 (0.37, 0.42)
Other	0.33 (0.30, 0.36)
Highest education level	
High school/GED	REF
None	0.98 (0.73, 1.29)
Grade school (K–8)	0.90 (0.82, 0.99)
Some college	1.04 (0.99, 1.09)
Assoc/bachelor's degree	1.10 (1.05, 1.15)
Postgraduate degree	1.11 (1.04, 1.18)
Unknown	0.98 (0.92, 1.04)
Dialysis before transplant	
No	REF
Yes	0.89 (0.86, 0.92)
Unknown	1.01 (0.92, 1.11)
Induction agent	
ATG	REF
None	0.82 (0.78, 0.87)
IL2RB	0.89 (0.85, 0.93)
CTSD	0.89 (0.84, 0.95)
2 agents	0.82 (0.75, 0.89)
Other	0.84 (0.56, 1.27)
Steroid	
Yes	REF
No	0.98 (0.94, 1.02)
Unknown	0.87 (0.81, 0.95)
Immunosuppression	
CNI+MMF	REF
None	0.73 (0.63, 0.85)
CNI	0.82 (0.76, 0.88)
MMF	0.99 (0.93, 1.07)
Other	0.92 (0.59, 1.45)
Date range by year	
2004–2007	REF
2008–2011	1.11 (1.06, 1.15)
2012–2016	1.14 (1.08, 1.20)

p Values for all variables were <0.005.
ATG, anti-thymoglobulin; CNI, calcineurin inhibitor; CTSD, cell-type specific depletion; IL2RB, interleukin-2 receptor blockade; MDO, myelodysplastic disorder; MMF, mycophenolate mofetil; NMSC, nonmelanoma skin cancer.

risk for patients with a history of hematopoietic malignancy (HR 2.00 CI 1.69, 2.36).

The primary causes of death for the 24,455 patients who died are listed in Table 5. More than 25% of the deaths were due to unknown causes. More patients with pre-TM died of malignancy-related complications than those without a history of pre-TM (19% vs 11%). Of the patients with pre-TM who died of cancer, 72 (16%) experienced a recurrence of their pre-TM before their death.

DISCUSSION

In the 22 years from 1994 to 2016, both the annual number and percentage of total kidney transplants being performed in patients with a pre-TM have increased more than 800%. The causes for the overall increase in pre-TM patients receiving kidney transplants are likely myriad, but include an aging US population[2] with more people living with kidney disease and cancer,[4,25] improvements in the treatment of cancer,[3] and more targeted immunosuppression regimens.[11] The apparent decrease in numbers and frequency of patients with pre-TM receiving kidney transplants in 2015 and 2016 may be related to implementation of the OPTN kidney allocation system in December 2014.[22]

Nonmelanoma skin cancer was the most common pre-TM in this population, consistent with NMSC being the most common cancer in the US.[26] This may be due to the fact that there is no recommended waiting time after curative treatment for patients with NMSC to receive a kidney transplant.[14] The high frequency of patients with NMSC, a disease more common in Caucasians,[27] may contribute to the higher frequency of white patients observed in the pre-TM group, although other causes for this difference cannot be excluded. Cancers with the highest incidence in the US, prostate and breast cancer,[3] were also well represented.

This study demonstrated that patients with a history of pre-TM have an increased risk of post-TM after their transplant. Our HR of 1.77 (CI 1.68, 1.86) is very similar to that reported in a recent meta-analysis by Acuna and colleagues[21] examining the risk of de novo malignancy developing in solid organ transplant recipients with a history of pre-TM (HR 1.92, CI 1.52, 2.42). It is likely that increased cancer screening in transplant patients with pre-TM contributes to this finding; however, there is no mechanism for us to evaluate this contribution. Although the number of post-TM in patients with pre-TM has increased during the study period, more patients without pre-TM developed post-TM. Indeed, the percentage of pre-TM patients who develop post-TM has remained fairly constant throughout our study period. Individuals with pre-TM appear to develop more NMSCs compared with those without pre-TM. This did not appear to be due to a high rate of NMSC recurrence because only 2% of patients with an NMSC as their pre-TM experienced a recurrence, although cancer recurrence rates are likely under-reported in UNOS. Nonmelanoma skin cancers are one of the most common cancers after transplantation,[6,28] which is confirmed in our analysis.

That lung cancer was the second most common post-TM was not surprising given the high incidence of lung cancer in the US population;[3] however, this result does contrast the finding of Engels and associates,[6] in which non-Hodgkins lymphoma (NHL) was found to be the second most common malignancy in patients with a history of pre-TM. This discrepancy is likely due to an era effect. Engels and coworkers[6] examined patients who underwent transplantation from 1987 to 2008, but did not include transplant year in their analysis. During this time period, the field of transplantation underwent extensive changes with respect to induction agents and immunosuppression agents. A recent study from the same group examined the incidence of non-Hodgkins lymphoma in the general transplant population over time; it found that the risk of developing this cancer was significantly lower in patients receiving transplants after 2004.[29] Our data reflect the lower likelihood of developing NHL in the more modern era of transplantation.

It was interesting that patients with a history of solid organ pre-TM had the lowest likelihood of developing post-transplant malignancies, but at the same time, were the majority (48%) of the recurrences that occurred. These data suggest that a history of solid organ malignancy before transplantation is significantly less likely to affect development of post-transplant malignancy compared with other pre-TMs. The high frequency of solid organ tumors in people who experienced recurrence is likely related to the high prevalence of solid organ tumors (70%) in the pre-TM patient population. An important caveat to this finding is that the solid organ category of malignancies is incredibly heterogeneous and includes cancers with widely differing recurrence rates, making interpretation complicated. It is more useful to examine the converse results: that patients with a history of NMSC, melanoma, or hematopoietic malignancies have an increased risk of post-TM malignancy. This suggests that the biologic factors driving these pre-TMs are at an increased risk of activation after transplantation. The importance of developing evidence-based cancer screening in the general transplant population was recently highlighted in an article by Acuna and coworkers[30] and an editorial by Blosser.[31] Our data suggest that patients with pre-TM may require even more vigilant cancer screening and that this screening should be broad, not solely focused on the pre-TM type.

Our analyses identified pre-TM as a contributing factor to both ACGF and DCGF. This is in contrast to a recent study by Dahle and colleagues,[20] which found no difference in overall graft failure, but improved DCGF in patients with pre-TM. The differences between these outcomes are likely accounted for by differences in study populations. Their population had different transplant indications, with a larger percentage of patients with autoimmune or inflammatory diseases (40% to 43% vs 5% to 9%) and fewer patients with diabetes (6% to 10% vs 21% to 25%). In addition, Dahle and associates[20] examined all kidney transplant recipients from 1963 through 2010—a time period that encompasses significant differences in induction and immunosuppression agents, all of which affect DCGF.[11] Finally, our study had a much larger and more diverse sample, of 11,691 pre-TMs out of 170,684 kidney transplants, compared with 377 pre-TMs out of 5,867 transplants, also likely contributing to differences.

The difference in risk of ACGF and DCGF likely reflects the impact of pre-TM on overall patient survival. This is evidenced by the similar HR for ACGF (HR 1.22 CI 1.18, 1.27) and patient survival (HR 1.23 CI 1.18, 1.28). Our finding that no sub-type of pre-TM was associated with increased risk of DCGF also supports this conclusion. These data demonstrate that pre-TM has a much larger impact on patient survival than graft function.

Pre-TM independently influences patient survival in our models (overall HR 1.23 CI 1.18, 1.28), consistent with other studies that have found pre-TM to be associated with worse overall patient survival for kidney and solid organ transplants.[21] Interestingly, the increased risk of death does not appear to be due solely to an increase in cancer-related deaths. Although a higher percentage of patients with pre-TM die of causes related to a malignancy than those without pre-TM, the majority of pre-TM patients are not dying of their malignancies,

Table 4. Multivariable Analysis of All Cause Graft Failure, Death Censored Graft Failure, and Patient Survival

Variable	All cause graft failure, hazard ratio (95% CI)	Death censored graft failure, hazard ratio (95% CI)	Patient survival, hazard ratio (95% CI)
Prior malignancy			
Any	1.22 (1.18, 1.27)	1.08 (1.02, 1.15)*	1.23 (1.18, 1.28)
NMSC	1.25 (1.14, 1.36)	1.10 (0.94, 1.30)†	1.19 (1.08, 1.32)
Melanoma	1.06 (0.91, 1.22)	0.87 (0.66, 1.14)†	1.08 (0.92, 1.27)
Blood/MDO	1.56 (1.35, 1.80)	1.06 (0.83, 1.36)†	2.00 (1.69, 2.36)
Solid organ	1.18 (1.12, 1.24)	1.08 (0.99, 1.17)†	1.18 (1.11, 1.25)
Unknown	1.32 (1.21, 1.45)	1.16 (0.99, 1.35)†	1.37 (1.23, 1.52)
Recipient age, y	1.01 (1.01, 1.01)	0.98 (0.98, 0.98)	1.05 (1.05, 1.05)
DGF	1.62 (1.59, 1.66)	1.87 (1.81, 1.93)	1.48 (1.43, 1.53)
Dialysis before transplant			
No	REF	REF	REF
Yes	1.40 (1.36, 1.44)	1.40 (1.34, 1.46)	1.39 (1.34, 1.45)
Unknown	1.15 (1.02, 1.29)	0.96 (0.80, 1.14)	1.35 (1.16, 1.57)
HLA mismatch	1.05 (1.04, 1.05)	1.08 (1.07, 1.08)	1.03 (1.02, 1.04)
Diabetes before transplant			
No	REF	REF	REF
Yes	1.42 (1.39, 1.45)	1.14 (1.11, 1.18)	1.82 (1.77, 1.87)
Unknown	1.11 (0.98, 1.27)	1.08 (0.91, 1.28)	1.17 (0.98, 1.41)
Induction agent			
ATG	REF	REF	REF
None	1.07 (1.04, 1.10)	1.02(0.98, 1.06)	1.11 (1.07, 1.15)
IL2RB	1.07 (1.05, 1.10)	1.04 (1.00, 1.08)	1.08 (1.04, 1.12)
CTSD	1.06 (1.03, 1.10)	1.12 (1.07, 1.17)	1.0 (0.99, 1.09)
2 agents	1.11 (1.06, 1.16)	1.12 (1.05, 1.19)	1.12 (1.06, 1.19)
Other	1.02 (0.82, 1.26)	1.15 (0.87, 1.52)	0.86 (0.63, 1.18)
Steroid			
Yes	REF	REF	REF
No	1.01 (0.98, 1.03)	1.07 (1.03, 1.10)	0.93 (0.90, 0.96)
Unknown	0.98 (0.95, 1.02)	1.06 (1.00, 1.12)	0.87 (0.82, 0.92)
Immunosuppression			
CNI+MMF	REF	REF	REF
None	2.95 (2.81, 3.09)	3.57 (3.36, 3.80)	2.27 (2.13, 2.43)
CNI	1.21 (1.17, 1.26)	1.20 (1.14, 1.27)	1.24 (1.18, 1.30)
MMF	1.27 (1.22, 1.32)	1.35 (1.25, 1.42)	1.19 (1.13, 1.25)
Other	1.22 (0.94, 1.57)	1.28 (0.90, 1.83)	1.02 (0.71, 1.46)
Date range by year			
2004−2007	REF	REF	REF
2008−2011	0.90 (0.88, 0.92)	0.89 (0.86, 0.91)	0.87 (0.85, 0.90)
2012−2016	0.77 (0.75, 0.80)	0.72 (0.69, 0.75)	0.76 (0.73, 0.79)

Additional variables in model included donor age, race, education, cold ischemic time, and donor type. p Values for all variables were <0.005 except where noted.

*p Value = 0.02 for development of any malignancy when examining death censored graft failure.

†p Value = 0.21 for variable of pre-TM malignancy type when examining death censored graft failure.

ATG, anti-thymoglobulin; CNI, calcineurin inhibitor; CTSD, cell-type specific depletion; DGF, delayed graft function; HLA, human leukocyte antigen; IL2RB, interleukin-2 receptor blockade; MDO, myelodysplastic disorder; MMF, mycophenolate mofetil; NMSC, nonmelanoma skin cancer.

consistent with a recently published report by Acuna and colleagues.[32] These data are limited by a high frequency of unknown causes of death. It is also notable that the majority of patients with pre-TM who die of cancer did not experience a recurrence of their pre-TM malignancy before death, although, as mentioned previously,

Table 5. Evaluation of Cause of Death in Entire Cohort

	No pre-TM (n = 22,090)		Pre-TM (n = 2,365)	
Cause of death	**n**	**%**	**n**	**%**
Unknown	6,448	29	602	25
Graft failure	216	1	27	1
Infection	3,598	16	328	14
Cardiovascular	4,202	19	386	16
Cerebrovascular	802	4	73	3
Hemorrhage	457	2	50	2
Malignancy	2,383	11	460*	19*
Trauma	243	1	32	1
Other	3,693	17	400	17
Missing	48	0	7	0

*72 of these patients (16%) experienced a recurrence of their pre-TM as classified by the United Network for Organ Sharing.
TM, transplant malignancy.

malignancy recurrence is likely under-reported in UNOS data. Given that pre-TM is a risk factor for developing post-TM malignancy, it is not surprising that in a population more likely to develop malignancy, a higher proportion of individuals in that population will die of malignancy compared with populations without this increased risk. A study looking specifically at cancer-related mortality in this population, similar to the recent studies published by D'Arcy and associates[33] and Noone and coauthors[34] linking cancer registries to UNOS, would be helpful in addressing this question.

Of the known pre-TM subtypes, transplant patients with a history of hematopoietic pre-TM had the highest risk of death when compared with transplant recipients without pre-TM (HR 2.00 CI 1.69, 2.36). Although limited literature exists on outcomes of patients who received solid organ transplants after hematopoietic stem cell transplants,[35-37] no study specifically examines outcomes in adult kidney transplant recipients. This likely reflects the small number of patients with a history of hematopoietic malignancy who undergo transplantation, and the fact that guidelines for evaluation of kidney transplant candidates do not include any recommendation for the patient with a history of hematopoietic cancer.[14] We do not know how many patients in our cohort were treated with stem cell transplants for their pre-TM; however, this study represents the largest number of patients with hematopoietic malignancies who subsequently underwent kidney transplantation studied to date.

A major limitation of this study is our inability to know how and when these patients were treated for their cancers. Unlike some studies using Scandinavian transplant registries,[19,20] we also did not know how much time elapsed between the patient's diagnosis of cancer and transplantation or the time they were deemed to be in remission and therefore eligible for transplantation. So we were unable to evaluate which guidelines were used for time from diagnosis to treatment. These are limitations of the UNOS database, and future studies using combined institutional or national cancer registries and UNOS data similar to those recently published using US and Canadian registries[32-34] could be used to address these limitations. The addition of a variable to the UNOS database that referenced when a patient with pre-TM entered remission or completed treatment would also facilitate future studies. Although we included induction agents and immunosuppression regimens at the time of discharge from the initial transplant hospitalization, we could not evaluate whether changes in immunosuppression regimens influenced our outcomes of interest. Additionally, screening recommendations, diagnostic testing, and treatment modalities for cancer have changed during the time period this study covers, potentially influencing diagnosis of post-TMs, graft failure from oncologic treatment, and patient survival. We could not evaluate the impact of these changes in our analysis.

CONCLUSIONS

This is the first study to examine long-term trends in kidney transplantation in patients with pre-TM. In this large national database analysis of more than 170,000 patients, we demonstrated that the past 2 decades have seen a dramatic increase in the numbers of patients with a history of malignancy who are receiving kidney transplants. As expected, these patients are at an increased risk of developing post-TM and at increased risk of graft failure.

The impact on overall patient survival remains complicated, but there does appear to be a decrease in survival associated with pre-TM, although this effect is smaller than the impact of other nonmalignancy factors. Taken in total, these data suggest that the current practices are effective in ensuring similar outcomes after transplantation in this patient population compared with patients without pre-TMs. However we were unable to evaluate whether the current guidelines of a 2- to 5-year tumor-free waiting period before kidney transplantation[14,15] are effective because UNOS does not collect data related to date of diagnosis, treatment, or remission for pre-TMs. Finally, the direct comparisons of different pre-TM subtypes and their impact on post-TM, ACGF, and DCGF presented here are novel. These results will aid physicians in providing more personalized advice to patients with ESRD and a history of previous malignancy with regard to the long-term outcomes of kidney transplantation.

Author Contributions

Study conception and design: Livingston-Rosanoff, Foley, Leverson, Wilke
Acquisition of data: Livingston-Rosanoff
Analysis and interpretation of data: Livingston-Rosanoff, Foley, Leverson, Wilke
Drafting of manuscript: Livingston-Rosanoff
Critical revision: Livingston-Rosanoff, Foley, Leverson, Wilke

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