Impact of Pre-Transplant Malignancy on Outcomes after Kidney Transplantation

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Introduction

- Increase in long term survival of malignancy
- Increase in the number of these patients
- Increase in population of patients with both ESRD and a previous cancer.
- Ageing of general population

Increasing rate of renal transplant

- The best treatment of ESRD : renal transplantation
- Better-targeted immunosuppressive agents
- Improvement in prophylaxis of infections
- Improvement in surgical technics
- Dramatic improvement in patients survival after age 65
- Use of ECD
- So more patients with more comorbities are candidate for transplant.

Introduction

- In previous studies recurrence of pre-TM was 1-25%
- Depends on study type and malignancy type
- Mortality risk in pre-TM was 2-3 times more than patients without history of cancer

Objective

1-Determine the frequency of kidney transplantation in patients with pre-TM over a 22 year period

2-Evaluate post-transplant outcomes of these transplant recipients

Method

Exclusion criteria

- Multi-organ transplant
- Unknown pre-TM status

Inclusion criteria

- All patients in 1994-2016 based on UNOS

Study population

United Network for Organ Sharing (UNOS) requires all solid organ transplants occurring in the United States

All kidney transplant since 1994-2016 (n=331,329)

Because of missing data patients between 2004-2016 were included in multivariate analysis (n=184,955)

- Patients with immediate graft failure (n=622) or who died on the day of transplant (n=96) were excluded from the analysis.

Analysis and statistics

- Primary outcome :
- All cause graft failure (ACGF)
- Death censored graft failure (DCGF)
- Overall patient survival

Recipient variables evaluated for post-TM

- Age, sex, race, education, body mass index (BMI), and whether the patient required dialysis prior to receiving their kidney transplant.

- Transplant-related variables included induction agent, maintenance immunosuppression/steroids prescribed at discharge from initial transplant hospitalization and year of transplant.

Method

- 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 that received two induction agents with different mechanisms of action were evaluated separately.

Method

- Maintenance immunosuppression medications:
- Calcineurin inhibitor (CNI; including cyclosporine and tacrolimus)
- Mycophenolate mofetil (MMF)
- Other agents

Time gategory

- To control for potential effects of transplants from different time periods, the years of transplantation evaluated in this study were divided into three eras:
- 2004–2007, 2008–2011, and 2012–2016.
- In preliminary univariate analysis all variables listed above, except for BMI (HR 1.00 CI 1.00, 1.00 p=0.79), were considered significant and included in the multivariable models.

method

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

method

- Panel reactive antibody (PRA) as a variable was not included because of missing from 28% (n=47,036) of the cohort.

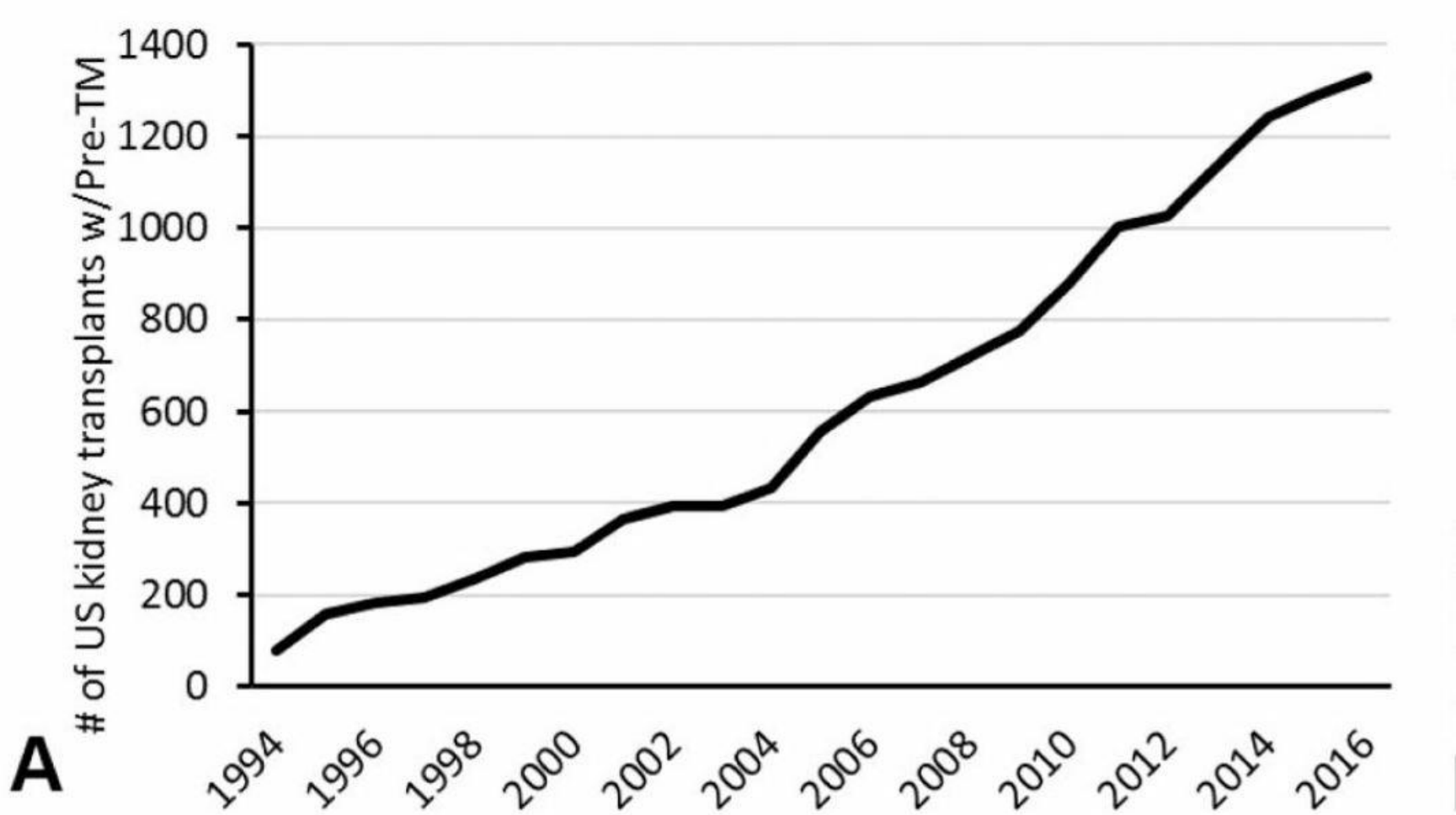
- Donor-specific variables included in analysis were age and type of donor (living vs deceased) as well as ECD status.

Method

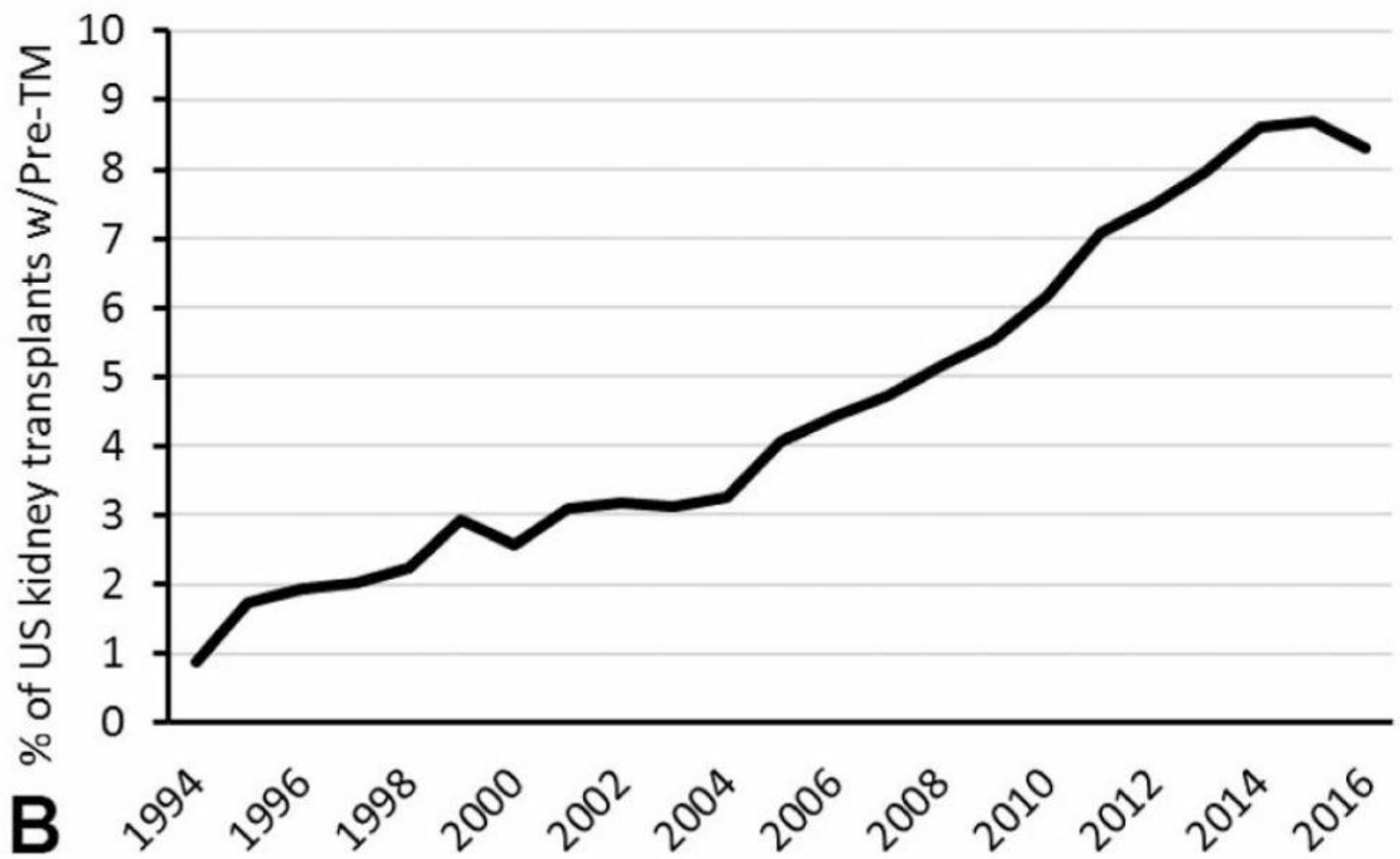
- **Transplant-specific variables**:
- cold ischemic time, induction agent, steroids and immunosuppression agents prescribed at the time of discharge from the initial transplant hospitalization, transplant era, and whether the patient experienced delayed graft function (DGF)

- DGF was defined as requiring dialysis within one week of kidney transplant

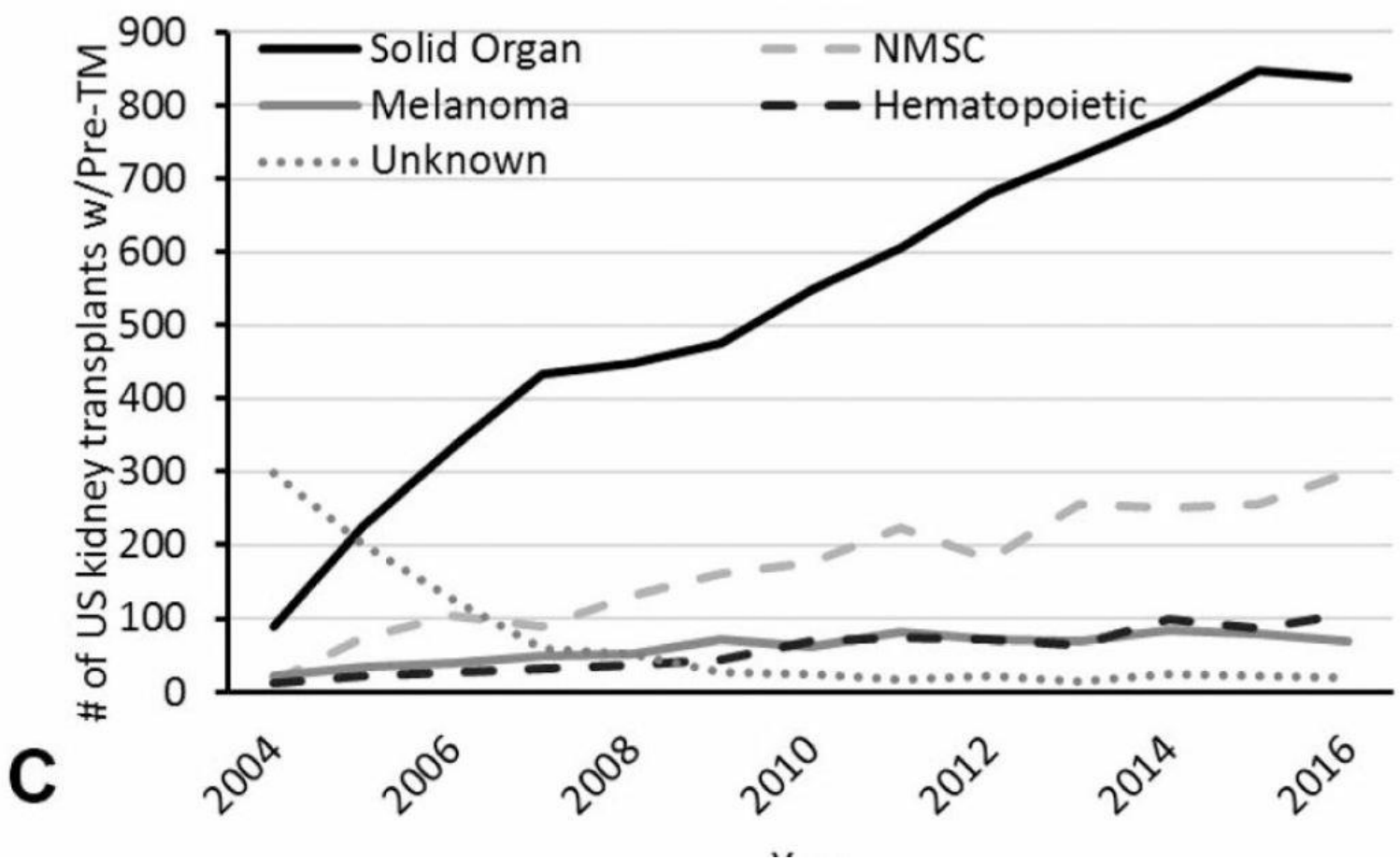
Total number of kidney Tx patients with pre TM



Percentage of patients with pre TM



Types of pre-TM



Demographic

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)
≥65y	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)

Demographic

11,691 kidney transplant recipients with pre-TM compared to 158,993 recipients without pre-TM who received their transplant from 2004–2016

Patients with pre-TM were **older** (median age 63y, range 18–89y vs median age 53y, range 18–96y)

Fewer had autoimmune/inflammatory diseases or diabetes listed as their transplant indication (5% vs 9%, $p<0.001$)

637 of 11691 patient with pre-TM had the malignancy as **cause of ESRD**

characterization

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 non-melanoma skin cancer (NMSC), 27 Hematopoietic, 110 solid organ/other, and 27 unknown.

Multivariable analysis

Variable	Hazard ratio (95% CI)
Prior 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)

Malignancy	Pre-TM		Post-TM			
	N = 12,798		No pre-TM, N = 18,611 *		Pre-TM, N = 3,016 †	
	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

Characterization of Pre- and Post-Transplant Malignancies

- Several patients had more than one 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%)
- Breast (7.7%), prostate (6.7%),
- Hematopoietic malignancies (6%).
- 2,268 cancers (17.7% of total cancers) were labelled as “GU cancers” and included in the “other” category in our analysis; 7% were unknown

Characterization of Pre- and Post-Transplant Malignancies

A total of 13,533 individuals in our cohort, 2,040 with pre-TM and 11,493 without pre-TM, developed 21,627 cancers following their kidney transplant

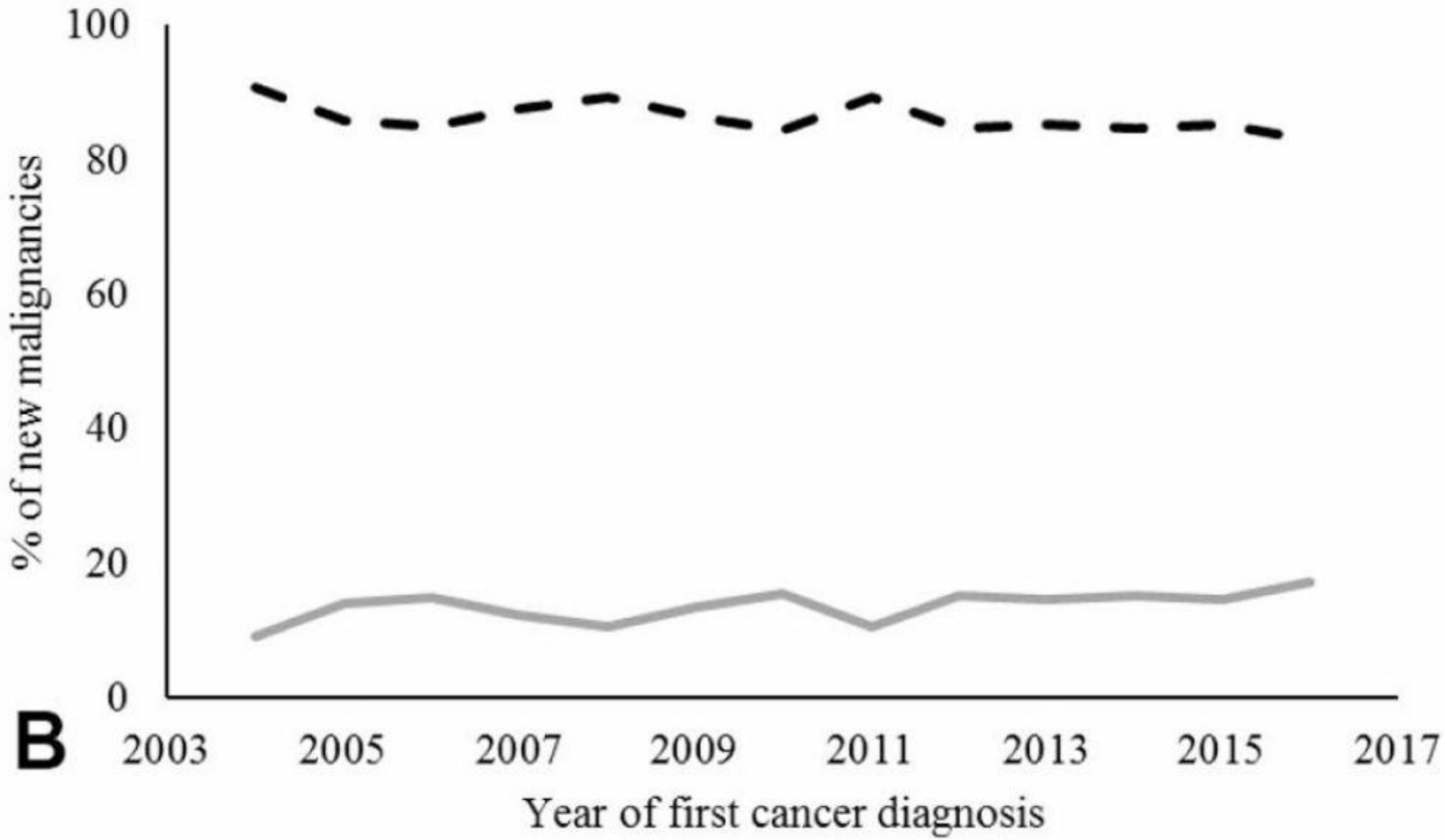
The 5y rate of post-TM in individuals with pre-TM was almost three times that of those without pre-TM (21.3% vs 7.3%).

NMSC 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%).

In our multivariable analysis pre-TM was strongly associated with the development of a post-TM with a HR of 1.77 (CI 1.68, 1.86)

Characterization of Pre- and Post-Transplant Malignancies

- 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%) were solid organ cancers followed by NMSC (21%), unknown (12%), hematopoietic (12%), and melanomas (7%).
- Patients with history of pre-TM were 10–15% of the total number of malignancies diagnosed in each year


100
80
60
40
20
0
% of new malignancies
B
2003
2005
2007
2009
2011
2013
2015
2017
Year of first cancer diagnosis

Cause of death	No pre-TM, N=22,090		Pre-TM, N=2,365	
	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

Evaluation of Cause of Death in Entire Cohort

- Over 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 prior to their death.

Multivariable analysis of Outcome

Variable	All cause graft failure, hazard ratio (95% CI)	Death censored graft failure, hazard ratio (95% CI)	Patient survival, hazard ratio (95% CT)
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)

Multivariable analysis of Outcome

- Pre-TM was associated with an increased risk of ACGF (HR 1.22 CI 1.18, 1.27)

- 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

Multivariable analysis of Outcome

- 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).

- 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.

Multivariable analysis of Outcome

- Pre-TM was independently associated with worse patient survival (HR 1.23 CI 1.18, 1.28)
- 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, while 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 risk for patients with a history of hematopoietic malignancy (HR 2.00 CI 1.69, 2.36).

DISCUSSION

- The causes for the overall increase in pre-TM patients receiving kidney transplants are likely myriad but include an **ageing** US population with more people living with kidney disease and cancer improvements in the treatment of cancer, and more targeted immunosuppression regimens.

- NMSC was the most common pre-TM in this population, consistent with NMSC being the most common cancer in the US

DISCUSSION

- This study demonstrated that patients with a history of pre-TM have an increased risk of post-TM after their transplant.
- The HR of 1.77 (CI 1.68, 1.86) is very similar to that reported in a recent meta-analysis by Acuna 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)
- Individuals with pre-TM appear to develop more NMSCs compared to those without PTM

DISCUSSION

- That **lung cancer** was the second most common post-TM was not surprising given the high incidence of lung cancer in the US population.
- This result does contrast the finding of Engels where non-hodgkins lymphoma (**NHL**) was found to be the second most common malignancy in patients with a history of pre-TM.

DISCUSSION

- This discrepancy is likely due to an era effect.
- Engels examined patients who underwent transplantation from 1987–2008 but did not include transplant year in their analysis.
- Extensive changes in induction agents and immunosuppression agents.
- A recent study from the same group examined the incidence of NHL in the general transplant population over time and found that the risk of developing this cancer was significantly lower in patients transplanted after 2004.
- Our data reflects the lower likelihood of developing NHL in the more modern era of transplantation.

DISCUSSION

- 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.

DISCUSSION

- This analyses identified pre-TM as a contributing factor to both ACGF and DCGF. This is in contrast to a recent study by Dahle that found no difference in overall graft failure, but improved DCGF in patients with pre-TM

- Their population had different transplant indications with a larger percentage of patients with autoimmune or inflammatory diseases (40–43% vs 5–9%) and fewer patients with diabetes (6–10% vs 21–25%).

DISCUSSION

- In addition, Dahle examined all kidney transplant recipients from 1963 through 2010 a time period that encompasses significant differences in induction and immunosuppression agents, all of which impact DCGF.
- Finally, this study had a much larger and more diverse sample of 11,691 pre-TMs out of 170,684 kidney transplants compared to 377 pre-TMs out of 5,867 transplants also likely contributing to differences.

Discussion

- 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

Conclusion

This analysis indicates that patients with pre-TM are at increased risk of post-TM, graft loss and decreased overall survival.

The studies 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

Thank you