HIGH RATES OF DE NOVO MALIGNANCY COMPROMISE POST-HEART TRANSPLANTATION SURVIVAL

Katherine Giuliano[1], Joseph Canner[1], Eric Etchill[1], Alejandro Suarez Pierre[2], Chun Choi[3], Robert Higgins[4], Steven Hsu[4], Kavita Sharma[4], and Ahmet Kilic[4]

[1]Johns Hopkins University School of Medicine
[2]University of Colorado Denver School of Medicine
[3]Johns Hopkins Medicine School of Medicine
[4]Johns Hopkins School of Medicine

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Abstract

Background: Transplant patients are known to be at increased risk of developing de novo malignancies (DNM). As heart transplant survival has increased, DNM represent an obstacle to further improving survival. We sought to examine the incidence, risk factors, and prognostic factors of post-transplant DNM. Methods: We studied adult heart transplant recipients from the Organ Procurement and Transplantation Network database (1987-2018). Kaplan-Meier survival analysis was performed to determine annual probabilities of developing DNM, excluding squamous and basal cell carcinoma. Rates were compared to the general population in the Surveillance, Epidemiology, and End Results database. Cox proportional hazards regression was performed to calculate hazard ratios for risk factors of DNM development, all-cause, and cancer-specific mortality. Results: Over median follow-up of 6.9 years, 18% of the 49,361 patients developed DNM, which correlated with an incidence rate 3.8 times that of the general population. The most common malignancies were lung, post-transplant lymphoproliferative disorder, and prostate. Risk was most increased for female genital, tongue/throat, and renal cancers. Male gender, older age, smoking history, and impaired renal function were risk factors for developing DNM, whereas the use of MMF for immunosuppression was protective. Cigarette use, increasing age, the use of ATG for induction and calcineurin inhibitors for maintenance were risk factors for cancer-specific mortality. The development of a DNM increased the risk of death by 40% ($p<0.001$). Conclusions: Heart transplant patients are at increased risk of malignancy post-transplant, particularly rare cancers. Strict cancer surveillance and attention to immunosuppressive regimens are critical for further prolonging post-transplant survival.

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Methods

We studied adult heart transplant recipients from the Organ Procurement and Transplantation Network database (1987-2018). Kaplan-Meier survival analysis was performed to determine annual probabilities of developing DNM, excluding squamous and basal cell carcinoma. Rates were compared to the general population in the Surveillance, Epidemiology, and End Results database. Cox proportional hazards regression was performed to calculate hazard ratios for risk factors of DNM development, all-cause, and cancer-specific mortality.

Results

Over median follow-up of 6.9 years, 18% of the 49,361 patients developed a DNM, which correlated with an incidence rate 3.8 times that of the general population. The most common malignancies were lung, post-transplant lymphoproliferative disorder, and prostate. Risk was most increased for female genital, tongue/throat, and renal cancers. Male gender, older age, smoking history, and impaired renal function were risk factors for developing DNM, whereas the use of MMF for immunosuppression was protective. Cigarette use, increasing age, the use of ATG for induction and calcineurin inhibitors for maintenance were risk factors for cancer-specific mortality. The development of a DNM increased the risk of death by 40% ($p<0.001$).

Conclusions

Heart transplant patients are at an increased risk of malignancy post-transplant, particularly rare cancers. Strict cancer surveillance and attention to immunosuppressive regimens are critical for further prolonging post-transplant survival.

INTRODUCTION

In 1969, Drs. Penn and Starzl first published their observation of five renal transplant patients who developed malignant lymphomas and cautioned about the risk of malignancy in transplant patients on long-term immunosuppression.[1] Since that time, many have published on the increased incidence of posttransplant malignancy compared to the general population, with immunosuppressive therapy and oncologic viral infections suggested as two causative etiologies.[2–5] These malignancies include lymphomas and the transplant-specific entity of post-transplant lymphoproliferative disorder (PTLD), as well as solid-organ malignancies. Post-transplant patients are at particularly increased risk of skin cancers, Kaposi sarcomas, and genitourinary carcinomas.[3,6]

Heart transplant patients are at even higher risk than other solid organ transplant recipients due to greater need for immunosuppression.[7,8] At the same time, post-heart transplant survival has improved over time with improvements in immunosuppression, infectious disease prophylaxis, perioperative care, and postoperative monitoring. The median survival for patients undergoing heart transplants between 2002 to 2009 is 12.5 years, an improvement from 10.5 years in 1992-2001.[9] The risk of post-transplant *de novo* malignancy (DNM) poses a threat to further survival improvement. Previous literature has suggested that calcineurin inhibitors specifically increase the risk of malignancy, whereas mycophenolate mofetil (MMF) and mTOR inhibitors decrease the risk.[8,10–12] We sought to examine rates of malignancy development in adult heart transplant patients, compare them to the general population, and identify potentially modifiable risk factors.

MATERIALS AND METHODS

Patient Population

After approval from the Johns Hopkins Institutional Review Board, we queried the Organ Procurement and Transplantation Network (OPTN) database for all adult (>18 years) heart transplant patients between October 1987 through September 2018. All data is deidentified (no informed consent). We excluded multi-organ transplant recipients, those without malignancy data (i.e. no post-transplant malignancy entry to correspond to transplant entry), and those with less than six months of follow-up. Among patients we identified who developed a post-transplant malignancy, we excluded a recurrence of a pre-transplant malignancy, squamous cell carcinoma, and basal cell carcinoma.

Statistical Analysis

Categorical and continuous characteristics were compared between heart transplant patients who developed DNM and those who did not using Pearson's chi-squared and two-sample t-tests. Kaplan-Meier survival analysis was performed to compute annual probabilities of developing DNM. Rates of malignancy – calculated per 100,000 person-years—were compared to the general population in the Surveillance, Epidemiology, and End Results (SEER) database using incidence ratios (IR).

Glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and categorized by stages I through V.[13,14] Cox proportional hazards regression

was performed to calculate hazard ratios (HR) with 95% confidence intervals (CI) for risk of DNM development, all-cause mortality, as well as cancer-specific mortality. For all statistical analyses, a p-value of <0.05 was considered statistically significant. Statistical analysis was performed using Stata version 14.2 (StataCorp, College Station, TX).

RESULTS

Study Population

A total of 49,361 heart transplant patients were included (**Figure 1**). Mean age was 51.9 years (SD 12.0), 76.7% (n=37,876) of recipients were male, and 75.4% (n=37,224) of patients were Caucasian. The most frequent etiology of heart failure leading to transplant listing was dilated myopathy in 72.8%. Pre-transplant comorbidities included 18.2% with diabetes, 0.5% with known prior malignancy, 22.2% with smoking history, and a mean GFR of 70.0 mL/min/1.73m^2 (SD 25.8) (**Table 1**).

Rate of Malignancy Development

Over a median follow-up period of 6.9 years (IQR 3.1-11.6 years), a total of 9,150 de novo malignancies (DNM) were diagnosed in 18.3% of patients (n=9,006) after heart transplantation. Malignancy was diagnosed, on average, 8.0 years (SD 5.3 years) after transplantation.

At one-year post-transplant, the incidence of DNM development was 1.4%. At three, five, and ten years post, malignancies developed in 5.6%, 10.2%, and 20.7% of patients, respectively (**Figure 2**).

The most common malignancies were lung (22.3%, incidence rate of 443 per 100,000 person-years), post-transplant lymphoproliferative disease (PTLD) (16.5%, 316 per 100,000 person-years), and prostate (16.4%, 425 per 100,000 person-years in men). Compared to the general population in the SEER database, the incidence ratio (IR) of developing any DNM status-post heart transplantation is 3.8. IRs were highest for female genital cancer (11.2), tongue/throat cancer (7.4), renal carcinoma (6.5), and esophageal cancer (6.2) (**Table 2**).

Risk Factors for Development of Malignancy

Male gender conferred a 24% increased risk of developing malignancy post-heart transplant (95% CI 1.17-1.31, p$<$0.001). (**Table 3**). Hispanic (HR 0.78, 95% CI 0.70-0.87) and Asian race (HR 0.68, 95% CI 0.55-0.84) were associated with lower risk of developing malignancy as compared to Caucasian race (p$<$0.001). Patients with DNM were older at the time of their transplant than patients without (53.8 vs. 51.4 years, p$<$0.001), with increasing age conferring a 2% increased risk of malignancy development (95% CI 1.02-1.03 p$<$0.001). A history of cigarette smoking also increased the risk by 39% (95% CI 1.27-1.53, p$<$0.001), as did recipient hepatitis B virus (HBV) core antibody positivity (HR 1.19, 95% CI 1.04-1.35, p=0.01). The average GFR at time of transplant of patients who later developed DNM was lower than those who did not (66.1 vs. 70.6 mL/min/1.73m^2, p$<$0.001) and requiring dialysis post-transplant particularly increased the risk of malignancy development (HR 1.17, 95% CI 1.03-1.33, p=0.01).

The use of induction therapy at the time of transplant was not associated with post-transplant malignancy on regression analysis (p=0.58), and this remained true when looking specifically at induction with basiliximab (p=0.70) or with anti-thymocyte globulin (ATG) (p=0.94) (**Table 3**). On Cox regression, the use of calcineurin inhibitors (p=0.07), mTOR inhibitors (p=0.09), and steroids (p=0.66) were not associated with malignancy risk, but MMF was associated with a reduced risk (HR 0.89, 95% CI 0.83-0.96, p=0.001).

Risk Factors for All-Cause Mortality

On last follow-up, 47.1% (n=23,251) of the patient cohort was deceased. African American race (HR 1.30, 95% CI 1.25-1.45, p$<$0.001), stage IIIb and IV CKD (HR 1.14, 95% CI 1.07-1.20 and HR 1.19, 95% CI 1.08-1.30, both p$<$0.001), diabetes (HR 1.32, 95% CI 1.27-1.37, p$<$0.001), tobacco use (HR 1.23, 95% CI 1.16-1.31, p$<$0.001), post-transplant stroke (HR 1.18, 1.05-1.33, p=0.005), and post-transplant dialysis (HR 1.29, 95% CI 1.20-1.38, p$<$0.001) were all associated with an increased risk of death (**Table 4**). The development

of a post-transplant DNM conferred a 43% increased risk of death (95% CI 1.38-1.47, p<0.001).**Figure 3** depicts the Kaplan-Meier survival estimates of patients with versus without DNM.

Risk Factors for Cancer-Specific Mortality

Just over 14% (n=3,291) of all deaths were directly attributable to cancer. Cigarette use (HR 1.37, 95% CI 1.16-1.62) and increasing age (HR 1.04, 95% CI 1.04-1.05) were specifically associated with cancer-specific mortality (CSM) (both p<0.001) (**Table 4**). The use of ATG (HR 1.15, 95% CI 1.03-1.30, p=0.03) or calcineurin inhibitors (HR 1.30, 95% CI 1.09-1.56, p=0.004) was associated with higher CSM, whereas steroid use was associated with lower CSM (HR 0.82, 95% CI 0.70-0.98, p=0.03).

CONCLUSIONS

In this study spanning three decades and nearly 50,000 heart transplant patients from the OPTN database, 18.3% of patients developed a post-transplant de novo malignancy (excluding non-melanoma skin cancers) an average of eight years after transplantation. While the most common malignancies were lung, PTLD, and prostate, the risk was most elevated for female genital, tongue/throat, renal, and esophageal cancer as compared to the general population. We found male gender, older age, smoking history, and impaired renal function to be risk factors for developing DNM, whereas the use of MMF for maintenance immunosuppression was protective. Cigarette use, increasing age, the use of ATG for induction and calcineurin inhibitors for maintenance were specifically risk factors for cancer-specific mortality. The development of a post-transplant malignancy increased the risk of death by 43%.

Our malignancy incidence rates of 18.3% over the entire follow-up period (median 6.9 years) and 10.2% at five years post-transplant largely agree with the published literature.[2,7,15–17]Youn et al. published the experience of 17,587 heart transplant patients from the International Society for Heart and Lung Transplantation (ISHLT) registry and found that 10.7% of patients developed a solid de novo malignancy by five years post-transplant.[15]Unique to our study is the large sample size and multi-institutional data, whereas many prior studies are from a single institution, and it is the first published report of DNM post-heart transplant in the OPTN database. Our median follow-up time was 6.9 years, yet malignancies were diagnosed, on average, eight years after transplantation. Hence, 18.3% may actually represent an underestimation of the true DNM rates with longer follow-up time.

Of the 9,150 DNMs diagnosed in patients followed in the OPTN database, the most common were lung in 22.3%, PTLD in 16.5%, and prostate in 16.4%. Notably, however, men formed the majority of this cohort (76.7%), increasing the prevalence of a male-specific malignancy like prostate cancer. Compared to the general population, post-heart transplant patients had a 5.3-times higher rate of developing lung cancer, whereas the IR of other common malignancies were not as elevated – 2.1 for prostate cancer (men only), 1.5 for breast cancer (women), and 1.6 for colorectal cancer. Kellerman et al., in a single-center study of 911 patients over 13 years, found similarly slightly increased SIRs for prostate, breast, and colorectal cancer (1.2, 2.4, and 1.0, respectively), but on the contrary also found a comparable risk of lung cancer (SIR 0.95).[18] Engels et al., however, in a 20-year study of solid organ transplant recipients from the U.S. Scientific Registry of Transplant Recipients (SRTR) database, reported a SIR of 2.57 for heart transplant patients developing lung cancer compared to the general population.[3]

Malignancies that are rare in the general population were much more prevalent in the post-transplant population, including female genital (IR 11.2), tongue/throat (IR 7.4), renal (IR 6.5), esophagus (IR 6.2), and male breast cancer (IR 5.6). This points to the importance of not only routine cancer surveillance—such as colonoscopy, mammography, and skin checks—but also heightened awareness of the possibility for less common malignancies in the transplant population.

Not surprisingly, we found increasing age and smoking history to be risk factors for development of a DNM and cancer-specific mortality, in keeping with findings from prior studies.[2,3,7,15,19,20] Age is a particularly important risk factor given that the average age of heart transplant recipients has been increasing for the past three decades, with median age at time of transplant now around 55 years.[9] In our analysis, increasing

GFR at the time of transplantation, representing better renal function, was associated with a decreased risk of DNM development and of all-cause mortality. Requiring dialysis post-transplant particularly increased risk. Increased cancer risk amongst end-stage renal disease (ESRD) patients has been previously described, attributed to dialysis-induced immune dysfunction and the ill effects of uremia such as impaired DNA repair.[21–23] Some cohort studies have also suggested increased malignancy risk in chronic kidney disease (CKD) not requiring dialysis.[24–26] Our current study confirms this risk in the post-heart transplant patient population and points to the need for particularly careful surveillance in heart transplant patients with CKD.

Much attention has been paid to immunosuppressive regimens and malignancy risk. In this patient cohort, 73.7% of patients received induction therapy. Induction therapy did not predict development of DNM, cancer-specific, or all-cause mortality, but there was increased all-cause mortality in patients who received basiliximab, and ATG increased the risk of cancer-specific mortality. Regarding maintenance immunosuppression, the use of MMF was associated with a lower risk of DNM and all-cause mortality but did not significantly decrease cancer-specific mortality. Taken together with evidence suggesting MMF has anti-tumor properties, these results support the preferential use of MMF for post-transplant immunosuppression with respect to DNM risk.[12] Calcineurin inhibitors, on the other hand, have been implicated in increasing cancer risk.[10,11]While in our analysis we did not see significantly increased risk of developing a DNM or of all-cause mortality, cancer-specific mortality was higher, supporting a move away from or at least caution and attention to surveillance and screening with calcineurin inhibitors. mTOR inhibitors were not associated with increased risk of DNM, all-cause, or cancer-specific mortality and might serve as an alternative immunosuppressive strategy in appropriately selected patients at higher risk for DNM development. While there is limited data on mTOR inhibitor use and DNM development (and only 1.8% of our cohort were on them), Asleh et al. reported a decreased risk of all DNM, PTLD, and non-melanoma skin cancers in patients converted from a calcineurin inhibitor-based to a sirolimus-based immunosuppressive regimen.[8]

This study is limited by its lack of granular data and sometimes large number of unknown clinical variables. For instance, infectious disease serology, which has important implications for cancer risk, was particularly under-reported (e.g. EBV serologic status was reported in only 52.3% of patients). These variables with high rates of unknown values should, therefore, be interpreted with caution given potential sampling bias.

In conclusion, the development of a DNM in heart transplant patients from the OPTN database increased the risk of death by 43%. Recipients were at the highest risk for malignancies that are rarer in the general population, such as female genital cancer and tongue/throat cancer. The use of ATG for induction and calcineurin inhibitors for maintenance immunosuppression increased risk for cancer-specific mortality, whereas MMF reduced the risk of developing a DNM. This represents one of the largest studies to date examining trends and risk factors for DNM after heart transplantation and points to the critical importance of strict follow-up that includes optimizing immunosuppressive regimens, routine cancer surveillance, and particular attention to the risk of rarer cancers in these patients.

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AUTHOR CONTRIBUTIONS

K Giuliano – concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article

J Canner – statistics, data analysis/interpretation, approval of article

E Etchill – concept/design, data analysis/interpretation, critical revision of article, approval of article

A Suarez-Pierre – concept/design, critical revision of article, approval of article

CW Choi – data analysis/interpretation, critical revision of article, approval of article

RSD Higgins – data analysis/interpretation, critical revision of article, approval of article

S Hsu – data analysis/interpretation, critical revision of article, approval of article

K Sharma – data analysis/interpretation, critical revision of article, approval of article

A Kilic – concept/design, data analysis/interpretation, critical revision of article, approval of article

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TABLES

Table 1. Characteristics of the entire cohort (n=49,361) of heart transplant recipients from the Organ Procurement and Transplantation Network database, 1987-2018.

Characteristic	**N (%)** Entire cohort: n=49,361
Mean **age**, years (SD)	51.9 (12.0)
Male **Gender**	37,876 (76.7%)
Race Caucasian African American Hispanic Asian Other Unknown	37,224 (75.4%) 7,492 (15.2%) 3,076 (6.2%) 1,078 (2.2%) 468 (1.0%) 23 (0.1%)
Diagnosis at Listing Dilated Myopathy Restrictive Myopathy Hypertrophic Myopathy Prior graft failure CAD Valvular Disease Congenital Other	35,915 (72.8%) 872 (1.8%) 811 (1.6%) 1,077 (2.2%) 7,611 (15.4%) 1,208 (2.5%) 1,030 (2.1%) 96 (0.2%)
Year Transplanted October 1987 – December 2004 January 2005 – September 2018	26,534 (53.8%) 22,827 (46.3%)
Comorbidities Mean BMI, kg/m^2 (SD)	26.3 (4.7)
Mean GFR, mL/min/1.73m^2 (SD) GFR >90 (CKD stage I) GFR 60-89 (CKD stage II) GFR 45-59 (CKD stage IIIa) GFR 30-44 (CKD stage IIIb) GFR 15-29 (CKD stage IV) GFR <15 (CKD stage V) Unknown	70.0 (25.8) 9,205 (18.7%) 15,838 (32.1%) 9,011 (18.3%) 5,149 (10.4%) 1,129 (2.3%) 167 (0.3%) 8,862 (18.0%)
Diabetes No Yes Unknown	29,925 (60.6%) 8,993 (18.2%) 10,443 (21.2%)
History of smoking No Yes Unknown	12,226 (24.8%) 10,960 (22.2%) 26,175 (53.0%)
Cerebrovascular disease No Yes Unknown	36,909 (74.8%) 1,776 (3.6%) 10,676 (21.6%)
History of Cancer No Yes Unknown	38,331 (77.7%) 269 (0.5%) 10,761 (21.8%)
Infectious Disease Serology HBV Core Antibody Negative Positive Unknown	35,430 (71.8%) 1,622 (3.3%) 12,309 (24.9%)

Characteristic	**N (%)** Entire cohort: n=49,361
HCV Serostatus Negative Positive Unknown	39,651 (80.3%) 838 (1.7%) 8,872 (18.0%)
CMV Status Negative Positive Unknown	11,660 (23.6%) 19,493 (39.5%) 18,208 (36.9%)
EBV Serostatus Negative Positive Unknown	3,375 (6.8%) 22,125 (44.8%) 23,861 (48.4%)
Post-Op Complications Stroke Yes No Unknown	676 (1.4%) 38,513 (78.0%) 10,172 (20.6%)
Dialysis Yes No Unknown	2,249 (4.6%) 36,964 (74.9%) 10,148 (20.6%)
Induction Therapy Basiliximab ATG	36,384 (73.7%) 6,113 (12.4%) 7,511 (15.2%)
Maintenance Therapy Calcineurin inhibitor	43,689 (88.5%) 896 (1.8%) 30,405 (61.6%) 43,171
mTOR inhibitor MMF Steroid	(87.5%)

SD: standard deviation, CAD: Coronary Artery Disease, BMI: Body Mass Index, GFR: Glomerular Filtration Rate, HBV: hepatitis B virus; HCV: hepatitis C virus; CMV: cytomegalovirus; EBV: Ebstein-Barr virus; ATG: anti-thymocyte globulin; MMF: mycophenolate mofetil

Table 2 . Incidence rates of malignancy by primary site in patients after heart transplantation and in the general population (from the Surveillance, Epidemiology, and End Results database)

Malignancy	**Rate, Heart Transplant Patients (per 100,000 person-years**
All sites Men	2244 2428 1621
Women	
Female genital	56
Post-transplant lymphoproliferative disorder (PTLD)	316
Lymphoma	
Tongue/throat	31
Renal carcinoma	118
Esophagus	39
Breast Men	7.9 289
Women	
Melanoma	150
Lung	443
Male genital	6.7
Kaposi sarcoma	10
Bladder	94
Larynx	16
Small intestine	7.8
Brain	21
Liver	20
Prostate (men)	425
Pancreas	33
Stomach	20
Colon/rectum	107
Leukemia	26
Thyroid	20
Ovary (women)	24
Uterus (women)	41
Testicle (men)	8.9

Table 3 . Characteristics of patients who developed a de novo malignancy (DNM) after heart transplantation

versus those who did not.

	Developed DMN (%) (n=9,006)	**Did not develop DMN (%) (n=40,355)**	**p value**	**Cox regression Hazard Ratio (95% CI)**	**p value**
Mean age, years (SD)	53.8 (10.1)	51.4 (12.3)	<0.001	1.03 (1.03-1.03)	<0.001
Male Gender	7,443 (82.6%)	30,433 (75.4%)	<0.001	1.24 (1.17-1.31)	<0.001
Race Caucasian	7,600 (84.4%)	29,624 (73.4%)	<0.001	Ref 1.05	0.2 <0.001
African	914 (10.1%) 336	6,578 (16.3%)		(0.97-1.13) 0.78	<0.001 0.4 0.7
American	(3.7%) 90 (1.0%)	2,740 (6.8%) 988		(0.70-0.87) 0.68	
Hispanic Asian	56 (0.6%) 10	(2.4%) 412		(0.55-0.84) 0.90	
Other Unknown	(0.1%)	(1.0%) 139		(0.69-1.17) 1.16	
		(0.03%)		(0.55-2.44)	
Diagnosis at	5,552 (61.6%) 96	30,363 (75.2%)	<0.001	Ref 0.99	0.9 0.02 0.001
Listing Dilated	(1.1%) 66 (0.7%)	776 (1.9%) 745		(0.80-1.21) 0.75	0.4 0.04 0.3 0.08
Myopathy	204 (2.3%) 2,591	(1.8%) 873		(0.59-0.96) 1.66	
Restrictive	(28.8%) 255	(2.2%) 5,020		(1.25-2.21) 1.03	
Hypertrophic	(2.8%) 91 (1.0%)	(12.4%) 953		(0.97-1.08) 0.88	
Prior graft	117 (1.3%)	(2.4%) 939		(0.77-0.99) 0.89	
failure CAD		(2.3%) 624		(0.72-1.10) 1.19	
Valvular Disease		(1.5%)		(0.98-1.44)	
Congenital					
Other					
Year Transplanted 1987 –2004 2005 – 2018				Ref 1.05 (0.87-1.27)	0.6
Comorbidities	25.8 (4.3) 66.1	26.5 (4.8) 70.6	<0.001 <0.001	1.00	0.3 <0.001 0.9
Mean BMI,	(23.9)	(26.0)	<0.001 <0.001	(1.00-1.01)	<0.001 0.8
kg/m^2 (SD)	1,057/4,930	7,936/33,988	<0.001	0.99	
Mean GFR,	(21.4%)	(23.3%)		(0.99-0.99)	
mL/min/1.73m^2	1,050/1,783	9,910/21,403		0.99	
(SD) Diabetes	(58.9%)	(46.3%)		(0.93-1.07)	
History	195/4,913	1,581/33,772		1.39	
smoking Cere-	(4.0%)	(4.7%)		(1.27-1.53)	
brovascular				0.98	
Disease				(0.85-1.13)	
Infectious	244/5,630	1,378/31,422	<0.001 <0.001	1.19	0.01 0.9 0.003
Disease	(4.3%)	(4.4%)	<0.001 <0.001	(1.04-1.35)	0.1
Serology HBV	118/6,112	720/34,377		1.01	
Core Ab (+)	(1.9%)	(2.1%)		(0.84-1.22)	
HCV (+)	1,957/3,136	16,251/26,732		0.56	
CMV (+)	(62.4%)	(60.8%)		(0.39-0.82)	
EBV (+)	2,186/2,845	19,939/22,955		0.91	
	(76.8%)	(86.9%)		(0.81-1.02)	

	Developed DMN (%) (n=9,006)	**Did not develop DMN (%) (n=40,355)**	**p value**	**Cox regression Hazard Ratio (95% CI)**	**p value**
Induction	6,104 (67.8%)	30,280 (75.0%)	<0.001 <0.001	0.98	0.6 0.7 0.9
Therapy	451 (5.0%) 909	5,662 (14.0%)	<0.001	(0.92-1.05)	
Basiliximab	(10.1%)	6,602 (16.4%)		0.98	
ATG				(0.88-1.09)	
				1.00	
				(0.93-1.08)	
Maintenance	6,918 (76.8%)	36,771 (91.1%)	<0.001 <0.001	0.91	0.07 0.09 0.001
Therapy	123 (1.4%)	773 (1.9%)	<0.001 <0.001	(0.82-1.01)	0.5
Calcineurin	3,249 (36.1%)	27,156 (67.3%)		0.85	
inhibitor	7,064 (78.4%)	36,107 (89.5%)		(0.71-1.03)	
mTOR				0.89	
inhibitor				(0.83-0.96)	
MMF Steroid				1.03	
				(0.94-1.13)	
Post-Op	82/5,050	594/4,139	<0.001 <0.001	1.00	1.0 0.01
Complications	(1.6%)	(1.7%)		(0.80-1.24)	
Stroke Dialysis	261/5,055	1,988/34,158		1.17	
	(5.2%)	(5.8%)		(1.03-1.33)	

Table 4. Association of patient and treatment factors with all-cause and cancer-specific mortality in heart transplant patients.

	Hazard Ratio, All-Cause Mortality (95% Confidence Interval)	p value	Hazard Ratio, Cancer-Specific Mortality (95% Confidence Interval)	p value
Development of DNM	1.43 (1.38-1.47)	<0.001		
Age	1.01 (1.01-1.0)	<0.001	1.04 (1.04-1.05)	<0.001
Male gender	0.99 (0.95-1.02)	0.4	1.06 (0.96-1.17)	0.3
Race Caucasian	Ref 1.30	<0.001 0.2 0.04	Ref 0.83	0.01 0.03 0.02 0.8
African American	(1.25-1.35) 0.96	0.3 0.8	(0.72-0.96) 0.79	0.08
Hispanic Asian	(0.90-1.02) 0.88		(0.64-0.98) 0.56	
Other Unknown	(0.78-0.99) 1.08		(0.34-0.90) 0.95	
	(0.93-1.25) 1.07		(0.60-1.52) 2.40	
	(0.64-1.78)		(0.89-6.48)	
Diagnosis at	Ref 1.07	0.3 <0.001 0.01	Ref 1.16	0.4 0.1 0.4 0.1 0.1
Listing Dilated	(0.95-1.21) 0.72	<0.001 0.001 0.7	(0.81-1.66) 0.68	0.05 0.5
Myopathy	(0.62-0.84) 1.29	0.6	(0.42-1.12) 0.76	
Restrictive	(1.06-1.56) 1.17		(0.43-1.35) 1.08	
Hypertrophic	(1.13-1.21) 0.87		(0.98-1.18) 0.85	
Prior graft failure	(0.80-0.95) 0.98		(0.68-1.06) 1.45	
CAD Valvular	(0.87-1.10) 0.96		(0.99-2.10) 1.11	
Disease	(0.84-1.10)		(0.80-1.55)	
Congenital Other				

	Hazard Ratio, All-Cause Mortality (95% Confidence Interval)	p value	Hazard Ratio, Cancer-Specific Mortality (95% Confidence Interval)	p value
Year Transplanted 1987 – 2004 2005 – 2018	Ref 1.08 (0.96-1.20)	0.2	Ref 1.09 (0.98-1.22)	0.1
Comorbidities	1.01 (1.01-1.01)	<0.001 <0.001	1.00 (0.99-1.01)	1.0 0.2 <0.001
BMI Higher GFR	0.99 (0.99-0.99)	0.03 0.1 <0.001	1.08 (0.97-1.21)	0.007
CKD stage II	0.95 (0.91-0.99)	<0.001 0.2 <0.001	1.37 (1.16-1.63)	
(*Ref stage I*)	1.04 (0.99-1.10)	<0.001 0.03	1.34 (1.08-1.66)	
Stage IIIa Stage	1.14 (1.07-1.20)			
IIIb Stage IV	1.19 (1.08-1.30)			
Stage V Diabetes	1.13 (0.92-1.39)			
History smoking	1.32 (1.27-1.37)			
Cerebrovascular	1.33 (1.20-1.48)			
Disease	1.09 (1.01-1.19)			
Infectious Disease	1.06 (0.98-1.15)	0.1 <0.001 0.8	1.09 (0.87-1.37)	0.4 0.2 0.7 0.5
Serology HBV	1.30 (1.17-1.43)	0.02	1.23 (0.92-1.66)	
Core Ab (+)	0.97 (0.76-1.22)		0.83 (0.35-1.96)	
HCV (+) CMV	0.92 (0.86-0.99)		1.07 (0.88-1.31)	
(+) EBV (+)				
Post-Op	1.18 (1.05-1.33)	0.005 <0.001	1.10 (0.78-1.55)	0.6 0.4
Complications	1.29 (1.20-1.38)		0.91 (0.73-1.13)	
Stroke Dialysis				
Induction	1.03 (0.99-1.08)	0.1 <0.001 0.5	1.10 (0.84-1.05)	0.3 0.06 0.01
Therapy	1.14 (1.07-1.22)		0.91 (1.00-1.43)	
Basiliximab ATG	1.02 (0.97-1.06)		1.15 (1.03-1.30)	
Maintenance	1.03 (0.97-1.10)	0.3 0.8 <0.001 0.6	1.30 (1.09-1.56)	0.004 0.2 0.2 0.03
Therapy	0.92 (0.83-1.01)		0.82 (0.60-1.13)	
Calcineurin	0.93 (0.89-0.97)		0.94 (0.84-1.05)	
inhibitor mTOR	0.98 (0.92-1.04)		0.83 (0.70-0.98)	
inhibitor MMF				
Steroid				

FIGURE LEGENDS

Figure 1. Study population of adult heart transplant recipients from the Organ Procurement and Transplantation Network database.

Figure 2 . Incidence of developing a *de novo* malignancy (DNM) over time after heart transplantation.

Figure 3 . Kaplan-Meier survival estimates comparing heart transplant patients who developed a post-transplant de novo malignancy (DNM) versus those who did not.