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Characteristics and outcomes of heart transplant recipients with a pretransplant history of malignancy

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We aimed to investigate the characteristics and outcomes of HTx recipients with a history of pretransplant malignancy (PTM). Among 1062 HTx recipients between 1997 and 2013, 73 (7.1%) patients had PTMs (77 cancer cases). We analyzed post-HTx outcome, recurrence of PTM, and development of de novo malignancies. Post-HTx outcome included overall survival, 10-year survival, 10-year freedom from cardiac allograft vasculopathy (CAV), non-fatal major adverse cardiac events (NF-MACE), any treated rejection (ATR), acute cellular rejection (ACR), and antibody-mediated rejection (AMR). Four most common PTMs were lymphoproliferative disorders (18.2%), prostate cancers (18.2%), non-melanoma skin cancers (18.2%), and breast cancers (13.0%). Median time from PTM and HTx was 9.0 years. During a median follow-up of 8.6 years after HTx, patients with PTM, compared to those without, showed significantly higher incidence of posttransplant malignancies (43.8% vs. 20.8%, $p < .001$) including 9.6% ($n = 7$) of PTM recurrences. However, patients with PTM, compared to those without, showed comparable overall survival, 10-year survival, 10-year freedom from CAV, NF-MACE, ATR, ACR, and AMR. Therefore, a history of PTM should not disqualify patients from HTx listing, while further research is necessary for early detection of posttransplant malignancies in these patients.

Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection; ATG, anti-thymocyte globulin; ATR, any treated rejection; CAV, cardiac allograft vasculopathy; CNI, calcineurin inhibitor; HTx, heart transplantation; ISHLT, international society for heart and lung transplantation; mTOR, mammalian target of rapamycin; NF-MACE, non-fatal major adverse cardiac events; NMSC, non-melanoma skin cancers; PTM, pre-transplant malignancy; UNOS, United Network for Organ Sharing.

Jong-Chan Youn and Darae Kim contributed equally to this paper as first authors.

KEYWORDS
heart transplant, posttransplant malignancy, pretransplant malignancy, prognosis, recurrence, survival

1 | INTRODUCTION

Heart transplant (HTx) is the optimal therapy for selected eligible patients with end-stage heart failure.[1,2] A history of pretransplant malignancy (PTM) has been considered as a relative contraindication for HTx because of the potential for recurrence or de novo malignancy development with immunosuppression, which may impact on post HTx survival.[2–10] However, the number of patients with prior malignancy needing HTx is increasing due to improved cancer survival and increasing numbers of effective, yet cardiotoxic cancer treatment regimen.[11–21] The adult heart recipient characteristics for the most recent era (2010 to June 2018) showed that 8.6% had a history of PTM.[22] However, detailed clinical characteristics and long-term posttransplant outcomes of these patients are largely unknown. Therefore, we sought to evaluate comprehensive characteristics and long-term outcomes of patients with PTM in consecutively enrolled HTx recipient cohort.

2 | METHODS

2.1 | Study population

This study is a single-center retrospective analysis to assess the characteristics and outcomes of HTx recipients with PTM. Among 1062 consecutively enrolled patients who underwent HTx between January 1997 and December 2013, 73 patients had a history of PTM (77 cancer cases). We investigated the clinical characteristics and long-term outcomes of patients with PTM ($n = 73$) compared to patients without PTM ($n = 989$) during the same study period. Our study complies with the Declaration of Helsinki and the study was approved by the Cedars-Sinai Institutional Review Board. Written informed consent was obtained from all enrolled patients.

2.2 | Immunosuppression

Induction therapy with anti-thymocyte globulin (ATG) was indicated for sensitized patients with panel reactive antibodies >10%, patients with renal insufficiency (creatinine >2 mg/dL), and patients receiving multiple organ transplants. Calcineurin inhibitor (CNI)-based triple immunosuppressive therapy (tacrolimus, mycophenolate mofetil, and prednisone) was administered initially as maintenance therapy to most patients. Cyclosporine was administered if patients developed severe side effects from tacrolimus, such as seizures or encephalopathy. A regimen using a mammalian target of rapamycin (mTOR) inhibitor, either sirolimus or everolimus, in place of the CNI (a CNI-free regimen) was prescribed for eligible patients, including those with renal insufficiency. An mTOR inhibitor replaced mycophenolate in conjunction with a CNI in patients who developed malignancy or other complications such as rejection with graft dysfunction, cytomegalovirus infection, or CAV. In case of intolerance to an mTOR inhibitor, a conventional CNI-based regimen was maintained. Patients at low risk for rejection were weaned off steroids 6 months after HTx. All HTx recipients underwent a protocol-based regular evaluation at transplantation clinic.[8]

2.3 | Clinical outcomes

Posttransplant clinical outcomes included overall survival, cause of death, 10-year survival, 10-year freedom from angiographic cardiac allograft vasculopathy (CAV, defined as any stenosis ≥30%), nonfatal major adverse cardiac events (NF-MACE, defined as myocardial infarction, percutaneous coronary intervention/angioplasty, new congestive heart failure, pacemaker/implantable cardioverter-defibrillator placement, and stroke), any treated rejection (ATR), acute cellular rejection (ACR, defined as biopsy-proven grade 2 or 3 cellular rejection), and antibody-mediated rejection (AMR, defined as biopsy-proven grade 2 or 3 antibody-mediated rejection). Types and frequencies of posttransplant malignancies including PTM recurrences were assessed as well.

2.4 | Statistical analysis

Categorical variables were summarized as frequency and percentage of the total group. Continuous variables were summarized as the mean ± standard deviation. Discrete variables were compared using the Chi-squared test. Continuous variables were compared using Student's *t*-test or Mann–Whitney test. The cumulative incidence of events was assessed using the Kaplan–Meier method and the statistical significance was calculated using the log-rank test. A *p*-value of <.05 was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 (IBM Corporation).

3 | RESULTS

3.1 | Clinical characteristics of patients with pretransplant malignancy

Among 1062 consecutively enrolled HTx recipients between 1997 and 2013, 73 (7.1%) patients (47 males, 58 ± 11 years) had PTMs (77 cancer cases). Detailed types and frequencies of PTMs are shown

in Table 1. Four most common malignancies were lymphoproliferative disorders (18.2%), prostate cancers (18.2%), non-melanoma skin cancers (NMSC) (18.2%), and breast cancers (13.0%). Median time from diagnosis of PTM and HTx was 9.0 years (25th–75th percentile range, 5.0–19.9 years) and every HTx had undergone with the clearance for PTM from oncologist consultation. All patients were in tumor remission for some time before being considered for transplantation. Because the time span varied depending on the type of malignancy, the decision by oncologists involved different genomic properties, tumor stages, and treatment opportunities/modalities. Baseline clinical characteristics of study population are shown in Table 2. Patients with PTM, compared to those without, were older with a higher proportion of female. Significantly more patients with PTM underwent induction therapy with ATG. Reasons for HTx included 13 cases (17.8%) of chemotherapy induced cardiomyopathy in patients with PTM.

3.2 | Types, frequencies, characteristics, and predictors of posttransplant malignancies

During a median follow-up of 8.6 years (25th–75th percentile range, 6.0–12.9 years) after HTx, malignancy developed in 43.8% (38 cancer cases/32 patients) of recipients with PTM. Of 38 post-HTx malignancy case, 31 cases were de novo malignancies and seven cases were PTM recurrences (Table 3). At the time of initial diagnosis of posttransplant malignancy, 12 (31.6%) cases showed multiple or extensive disease status. While most of the cancers (n = 32, 84.2%) were surgically resected at the initial presentation, over one-third of cancers (n = 13, 34.2%) showed recurrence or disease progression (Table 3). Detailed clinical history of seven recurred cases (four squamous cell carcinomas, one renal cell carcinoma, one prostate cancer, and one breast cancer) are shown in Table 4.

When compared to those without PTM, HTx patients with PTM showed significantly higher incidence of posttransplant malignancy

TABLE 1 Types and frequencies of pretransplant malignancies in heart transplant recipients

Types of cancer	Total (n = 77)
Lymphoproliferative disorder	14 (18.2%)
Prostate cancer	14 (18.2%)
Breast cancer	10 (13.0%)
NMSC—Basal cell carcinoma	8 (10.4%)
NMSC—Squamous cell carcinoma	6 (7.8%)
Cervical cancer	4 (5.2%)
Leukemia	4 (5.2%)
Colorectal cancer	2 (2.6%)
Renal cell cancer	2 (2.6%)
Thyroid cancer	2 (2.6%)
Neuroendocrine cancer	2 (2.6%)
Brain cancer	2 (2.6%)
Endometrial cancer	2 (2.6%)
Others (melanoma, lung, bladder, larynx, ovary)	5 (6.5%)

Abbreviation: NMSC, non-melanoma skin cancer.

TABLE 2 Baseline characteristics of patients with or without PTM

Variables	PTM (n = 73)	Without PTM (n = 989)	p-value
Recipient demographic and transplantation variable			
Age (years)	57.8 ± 10.8	55.0 ± 12.5	.034
Female (%)	26 (35.6%)	242 (24.5%)	.049
Race			.458
Caucasian/White	59 (80.8%)	718 (72.6%)	
Black	7 (9.6%)	117 (11.8%)	
Latino/Hispanic	4 (5.5%)	78 (7.9%)	
Asian/Pacific Islander	3 (4.1%)	76 (7.7%)	
Reasons for transplant (%)			<.001
Ischemic	34 (46.6%)	453 (45.8%)	
Idiopathic	20 (27.1%)	360 (36.4%)	
Chemotherapy induced	13 (17.8%)	0 (0%)	
Congenital	4 (5.5%)	85 (8.6%)	
Amyloid	1 (1.4%)	24 (2.4%)	
Sarcoid	0 (0%)	5 (0.5%)	
Others	1 (142%)	62 (6.3%)	
BMI (kg/m^2)	24.9 ± 4.2	25.1 ± 4.4	.714
Hypertension (%)	31 (42.5%)	371 (37.5%)	.453
Diabetes (%)	22 (30.1%)	236 (23.9%)	.257
Pretransplant MCS (%)	15 (20.5%)	173 (17.5%)	.525
Multiorgan transplant (%)	7 (9.6%)	63 (6.4%)	.322
Pregnancy history (%)	19 (26.0%)	181 (18.3%)	.120
Induction therapy with ATG (%)	40 (54.8%)	365 (36.9%)	.033
High-risk CMV mismatch (%)	16 (22.5%)	210 (26.6%)	.113
Total ischemic time (minutes)	173.9 ± 60.8	188.8 ± 62.6	.050
Hospital stay (days)	18.3 ± 26.5	15.9 ± 15.5	.448
ICU stay (days)	8.1 ± 8.1	7.7 ± 7.0	.692
Donor variables			
Donor age (years)	32.2 ± 12.6	32.9 ± 12.6	.496

Note: Values are mean ± SD or number (%). Categorical variables were compared using the chi-squared method, and independent t-tests were used for the continuous variables.

Abbreviations: ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; ICU, intensive care unit; MCS, mechanical circulatory support; PTM, pretransplant malignancy.

TABLE 3 Types, frequencies, and outcomes of posttransplant malignancies in patients with PTM

Types of cancer	Numbers	Multiple or extensive disease	Surgical resection	Recurrence or disease progression
Skin—NMSC: Squamous cell carcinoma	20 (52.6%)	6 (30.0%)	20 (100%)	6 (30.0%)
Skin—NMSC: Basal cell carcinoma	4 (10.5%)	1 (25.0%)	4 (100%)	0 (0%)
Skin—Melanoma	1 (2.6%)	1 (100%)	1 (100%)	0 (0%)
Lung cancer	4 (10.5%)	2 (50.0%)	1 (25.0%)	3 (75.0%)
Breast cancer	2 (5.3%)	0 (0%)	2 (100%)	0 (0%)
Renal cell carcinoma	2 (5.3%)	0 (0%)	2 (100%)	1 (50.0%)
Bladder cancer	2 (5.3%)	0 (0%)	2 (100%)	1 (50.0%)
Prostate cancer	1 (2.6%)	1 (100%)	0 (0%)	1 (100%)
Lymphoproliferative disorder	1 (2.6%)	0 (0%)	0 (0%)	1 (100%)
Neuroendocrine cancer	1 (2.6%)	1 (100%)	0 (0%)	0 (0%)
Skin cancers	25 (65.8%)	8 (32.0%)	25 (100%)	6 (24.0%)
Non-skin cancers	13 (34.2%)	4 (30.8%)	7 (53.8%)	7 (53.8%)
Total	38 (100%)	12 (31.6%)	32 (84.2%)	13 (34.2%)

Abbreviation: NMSC, non-melanoma skin cancer.

TABLE 4 Detailed clinical history of seven recurred cancer cases after HTx

Sex/age	Original cancer	Time to HTx	Time to recur	Recurred cancer	Leading to mortality
M/64	Renal cell carcinoma	66 months	67 months	Renal cell carcinoma with femur and lung metastasis	Yes
M/45	NMSC (SCC), leg	76 months	20 months	NMSC (SCC), face	No
M/45	Prostate cancer	9 months	17 months	Prostate cancer with bone metastasis	Yes
M/58	NMSC (SCC), forearm	7 months	40 months	NMSC (SCC), abdomen	No
F/65	Breast cancer	101 months	44 months	Breast cancer with chest wall and axillary node metastasis	Yes
M/68	NMSC (SCC), earlobe	17 months	29 months	NMSC (SCC), cheek	No
M/67	NMSC (SCC), wrist	96 months	25 months	NMSC (SCC), forearm	No

Abbreviations: HTx, heart transplant; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma.

(43.8% vs. 20.8%, $p < .001$). Posttransplant malignancy risk was not different according to types of PTM (skin cancer vs. non-skin cancer: 61.5% vs. 40.0%, $p = .134$). However, among patients with PTM, patients with skin cancer history, compared to those with non-skin cancer history, showed a numerically higher risk of developing skin cancer after HTx (87.5% vs. 58.3%, $p = .141$), although it did not affect post-HTx survival outcome. Clinical characteristics of patients with PTM according to the development of posttransplant malignancy are shown in Table 5. In subgroup of patients with PTM, patients who developed posttransplant malignancy showed higher body mass index and were more likely to be male and of white race, as compared to those who did not develop posttransplantation malignancy. However, time from PTM to HTx was not different between two groups (Table 5). White race was an independent predictor for overall posttransplant malignancy and posttransplant skin cancer (Table 6).

3.3 | Clinical outcomes of patients with pretransplant malignancy

HTx recipients with PTM ($n = 73$) showed comparable long-term post-HTx outcome to those without PTM ($n = 989$), including overall survival, 10-year survival, 10-year freedom from CAV, NF-MACE, ATR, ACR, and AMR (Figure 1, Table 7). Patients with PTM had a numerically lower 10-year freedom from CAV and ACR than those without PTM. Even with significantly higher incidence of posttransplant malignancy, there was no adverse impact on post-HTx outcomes in terms of morbidity and mortality. In subgroup analysis, patients with PTM were further divided according to the development of posttransplant malignancy or PTM recurrence. Among patients with PTM, long-term clinical outcomes were comparable regardless of posttransplant malignancies or recurrence of PTM (Supplementary Tables S1 and S2).

TABLE 5 Baseline characteristics of patients with PTM according to the development of posttransplant malignancy

Variables	Posttransplant malignancy ($n = 32$)	No posttransplant malignancy ($n = 41$)	p-value
Recipient age (years)	57.7 ± 12.5	57.9 ± 9.5	.929
Recipient male gender (%)	25 (78.1%)	22 (53.7%)	.048
Recipient race			.017
Caucasian/White	31 (96.9%)	28 (68.3%)	
Black	0 (0%)	7 (17.1%)	
Latino/Hispanic	1 (3.1%)	3 (7.3%)	
Asian/Pacific Islander	0 (0%)	3 (7.3%)	
Reasons for transplant (%)			.053
Ischemic	18 (56.3%)	19 (46.3%)	
Idiopathic	8 (25.0%)	14 (34.1%)	
Congenital	5 (15.6%)	1 (2.4%)	
Amyloid	1 (3.1%)	1 (2.4%)	
Others	0 (0%)	6 (14.6%)	
BMI (kg/m^2)	26.1 ± 3.5	24.0 ± 4.5	.037
Hypertension (%)	12 (37.5%)	19 (46.3%)	.483
Diabetes (%)	13 (40.6%)	9 (22.0%)	.123
Pretransplant MCS (%)	6 (18.8%)	9 (22.0%)	.779
Multiorgan transplant (%)	4 (12.5%)	3 (7.3%)	.692
Pregnancy history (%)	6 (18.8%)	13 (31.7%)	.285
Donor age (years)	36.0 ± 13.5	36.4 ± 13.8	.900
Induction therapy with ATG (%)	19 (59.4%)	21 (51.2%)	.364
High-risk CMV mismatch (%)	11 (34.4%)	5 (12.8%)	.063
Total ischemic time (minutes)	169.2 ± 51.3	177.6 ± 67.7	.563
Hospital stay (days)	16.4 ± 12.6	19.7 ± 33.3	.612
ICU stay (days)	7.6 ± 5.0	8.4 ± 9.5	.708
Time from PTM to HTx (years)	13.2 ± 12.5	12.5 ± 9.9	.775

Note: Values are mean ± SD or number (%). Categorical variables were compared using the chi-squared method, and independent *t*-tests were used for the continuous variables.

Abbreviations: ATG, anti-thymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; HTx, heart transplant; ICU, intensive care unit; MCS, mechanical circulatory support; PTM, pretransplant malignancy.

In subgroup analysis, we classified patients with PTM into two groups according to the time interval between cancer diagnosis and HTx (Supplementary Table S3). Clinical outcomes, including posttransplant malignancy, recurrence of PTM, 10-year and overall survival were similar between PTM with time interval between cancer diagnosis and HTx <5 years and ≥5 years.

4 | DISCUSSION

Aging population and improved cancer treatment have resulted in a growing number of cancer survivors.[10,18,19] The number of patients with prior malignancy needing HTx is also increasing due to increased numbers of cancer survivors and cardiotoxic cancer treatment.[12–19] Recent registry data from the United Network for Organ Sharing (UNOS) revealed that early survival of patients with PTM was poorer driven by increased mortality for patients with hematologic PTM, but mortality at 5 year of PTM was comparable between those with and without PTM.[23] However, detailed clinical characteristics and comprehensive outcomes including CAV, NF-MACE, ATR, ACR, and AMR have not been investigated.

In this study, among 1062 consecutively enrolled HTx recipients between 1997 and 2013, 73 (7.1%) patients had PTMs (77 cancer cases). The incidence of PTM in our cohort is similar to previous reported studies, including the international society for heart and lung transplantation (ISHLT) registry (8.7%), the contemporary UNOS data (7.7%), and Korean transplantation registry data (7%).[7,23,24] The four most common PTMs were lymphoproliferative disorders, prostate cancers, non-melanoma skin cancers, and breast cancers. Median time from diagnosis of PTM to HTx was 9.0 years and patients with PTM were followed for a median follow up duration of 8.6 years after HTx. Patients with PTM, compared to those without, showed significantly higher incidence of posttransplant malignancies (43.8%) including 9.6% of PTM recurrences. However, patients

TABLE 6 Multivariable logistic regression analysis[a] for posttransplant malignancy development

	Posttransplant malignancy					
	Overall		Skin cancer		Non-skin cancer	
Variables	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age at HTx	0.97 (0.91–1.02)	.198	0.98 (0.95–1.01)	.229	1.00 (0.96–1.04)	1.000
Male	2.41 (0.67–8.67)	.178	1.78 (0.82–3.80)	.146	1.21 (0.43–3.39)	.718
White race	10.29 (1.19–89.07)	.034	8.88 (3.25–24.3)	<.001	1.02 (0.932–1.11)	.072
BMI	1.11 (0.98–1.27)	.109	0.91 (0.85–0.98)	.009	1.02 (0.93–1.11)	.687
Induction therapy with ATG	0.83 (0.606–1.14)	.205	0.58 (0.32–1.03)	.061	0.93 (0.43–2.02)	.848

Abbreviations: BMI, body mass index; CI, confidence interval; HTx, heart transplantation; OR, odds ratio.

[a]Multivariable regression analysis were adjusted with induction therapy, pre-HTx comorbidities (hypertension, diabetes), and high-risk CMV mismatch.

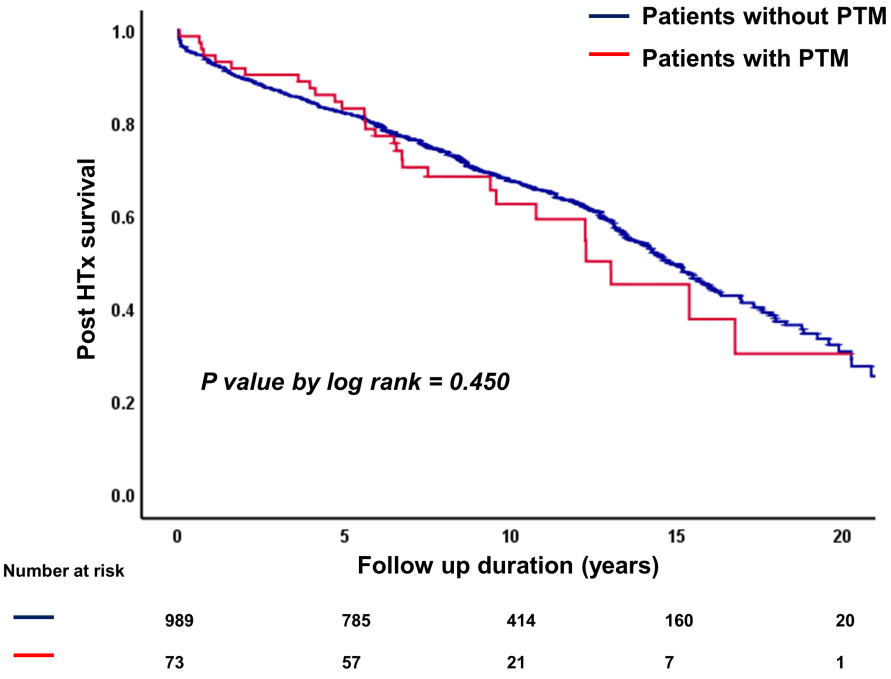

FIGURE 1 Cumulative Kaplan–Meier estimates of survival in patients with or without pretransplant malignancy. HTx, heart transplant; PTM, pretransplant malignancy [Color figure can be viewed at wileyonlinelibrary.com]

with PTM showed comparable overall survival, 10-year survival, 10-year freedom from CAV, NF-MACE, ATR, ACR, and AMR, compared to those without PTM, similar to results from the contemporary UNOS data.[23]

Current ISHLT guidelines require 5 years of freedom from cancer before HTx listing.[25] In our cohort, the most patients had significant period of elapse between (the median time from PTM to HTx was 9.0 years) their PTM and HTx. Among patients with PTM, 18 patients (24.6%) underwent HTx within 5 years from their PTM. Their PTM included squamous cell skin cancer (n = 3), basal cell skin cancer (n = 5), prostate cancer (n = 6), colorectal cancer (n = 1), bladder cancer (n = 1), thyroid cancer (n = 1), and endometrial cancer (n = 1). Non-melanoma skin cancer was the most common PTM (n = 8) in this group of patients. The rest of patients with other solid malignancies had undergone curative resection and had no evidence of residual malignancies at the time of HTx eligibility evaluation based on imaging studies. As a subgroup analysis, clinical outcomes, including posttransplant malignancy, recurrence of PTM, and 10-year and overall survival were not significantly different between PTM with time interval between cancer diagnosis and HTx <5 years and ≥5 years. HTx should be considered when cancer recurrence is low based on cancer type, response to therapy, and without evidence of metastasis. A history of PTM should not disqualify patients from HTx listing and specific amount of time to wait to transplant after cancer remission will depend on the aforementioned factors.[25] In our center, heart failure patients with previous history of malignancies are screened by their oncologists to determine the risk of cancer recurrence, and, generally, only those with expected 5-year cancer-free survival ≥70% undergo evaluation for HTx.

Whereas all HTx recipients are at a high risk for posttransplant malignancy,[5,6] patients with PTM have a higher risk of posttransplant malignancy, compared to those without PTM. Underlying mechanisms are unclear but may be related to an increased genetic susceptibility toward further additional malignancies in those with PTM or potentially due to an immune dysfunction related to cancer therapy. Recurrent of PTM occurred in seven patients (9.6%) and

TABLE 7 Clinical outcome of patients with or without PTM

Variables	PTM ($n = 73$)	Without PTM ($n = 989$)	p-value
Mortality outcomes			
Number of deaths	29 (39.7%)	413 (41.8%)	.806
Cause of deaths			.307
Cardiac	6 (20.7%)	143 (34.6%)	
Infection	9 (31.0%)	87 (21.1%)	
Malignancy	5 (17.2%)	48 (11.6%)	
Renal	2 (6.9%)	18 (4.4%)	
Cerebrovascular	2 (6.9%)	12 (2.9%)	
Others	5 (17.2%)	105 (25.4%)	
Overall survival	60.3%	58.2%	.450
10-year survival	68.5%	70.4%	.571
Morbidity outcomes			
CAV	25 (34.2%)	255 (25.8%)	.130
NF-MACE	18 (24.7%)	266 (26.9%)	.784
ATR	17 (23.3%)	181 (18.3%)	.279
ACR	11 (15.1%)	93 (9.4%)	.149
AMR	7 (9.6%)	70 (7.1%)	.479
10-year freedom from CAV	68.5%	76.6%	.062
10-year freedom from NF-MACE	78.1%	76.0%	.703
10-year freedom from ATR	76.7%	81.9%	.191
10-year freedom from ACR	84.9%	90.7%	.085
10-year freedom from AMR	90.4%	93.2%	.371

Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection; ATR, any treated rejection; CAV, cardiac allograft vasculopathy; NF-MACE, non-fatal major adverse cardiac events defined as myocardial infarction, percutaneous coronary intervention/angioplasty, new congestive heart failure, pacemaker/implantable cardioverter–defibrillator placement, and stroke.

three of recurred PTM cases were related to mortality. However, overall post-HTx clinical outcome was similar between patients with and without PTM. Previous studies using UNOS registry showed a higher mortality rate among HTx patients with pretransplant history of hematologic malignancy.[14] However, in our cohort, post-HTx mortality was not increased in patients with previous history of lymphoproliferative disorder (HR 1.05, 95% CI 0.363–1.036, $p = .925$). Our findings suggest that a history of PTM should not disqualify patients from HTx listing, given comparable 10-year and overall survival after HTx to those without PTM, and meticulous interdisciplinary consultation with oncologists may improve HTx outcomes in patients with PTM. However, a significantly higher incidence of posttransplant malignancy in patients with PTM highlights the need for future research on effective strategies for appropriate surveillance for posttransplant malignancies in patients with PTM. It is imperative to counsel with oncologists on selecting the appropriate HTx candidates with PTM in a safe manner and weigh the risk of posttransplant malignancies including cancer recurrence against the benefit from HTx.

In our cohort, significantly more patients with PTM received induction therapy with ATG compared to those without PTM. Despite potential risk of malignancy development after transplantation, decision for induction therapy with ATG was based on recipient's immunologic risks, as every HTx recipient with PTM underwent evaluation by an oncologist prior to listing for transplantation.[26–28] Despite higher incidence of induction therapy with ATG in PTM group, long-term transplantation outcome was similar between those with and without PTM. Our finding may support safety and efficacy of induction therapy with ATG, even in patients with PTM. In our cohort, maintenance immunosuppression in patients with PTM was not different from those without PTM. An mTOR inhibitor was considered for those with renal insufficiency, malignancy, rejection with graft dysfunction, cytomegalovirus infection, or CAV, unless contraindicated. We found no significant association between posttransplantation malignancies and induction therapy or immunosuppressive regimen after HTx. Similar to our study, previous studies suggested that there was no variation or alterations of immunosuppressive regimen to maintain graft function in patients with PTM.[14,29] Well-designed translational studies are necessary to determine the role of specific immunosuppressive agents on the development of posttransplant malignancies.

4.1 | Limitations

This study has several potential limitations. First, our study population cannot represent all HTx recipients with PTM. Although the patients were consecutively enrolled, it cannot be free from the limitation of a single-center observational study. Due to a relatively small number of patients in the PTM group, there is a possibility of a type II error and our results need to be interpreted with caution. However, the incidence of PTM was similar to that of other large transplant registries, including the recent ISHLT data.[24] Second, cancer-related detailed information were not fully standardized due to varied types and stages of each cancer. Third, we were unable to make any conclusions about the role of specific immunosuppressive agents on the development of posttransplant malignancies due to limited number of patients with PTM and diverse immunosuppression regimens and their changes during the follow-up period.

5 | CONCLUSION

Even with pretransplant history of malignancy, carefully selected HTx recipients showed comparable clinical outcome with patients without PTM including overall survival, 10-year survival, 10-year freedom from CAV, NF-MACE, ATR, ACR, and AMR, despite higher

incidence of posttransplant malignancy. A history of PTM should not disqualify patients from HTx listing, while further research is necessary for prevention and early detection of posttransplant malignancies in these patients.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. D.H.C. received research grants from Amgen, Biocardia, and Mesoblast and has moderate stock interest in Abbott Laboratories, Abbvie Inc, Repligen Corporation, Amarin Corporation, and Portola Pharmaceuticals. J.K.P. received research grants from Alexion Pharmaceuticals, Pfizer, Alnylam Pharmaceuticals, and Astra Zeneca. D.R. received research grants from Abiomed, Cardiac Assist, Inc., and Thoratec LLC.; consultancy fees from Abbott Laboratories and Baxter Healthcare; and nonfinancial support from Medtronic Vascular. F.E. received research grant from TransMedics Inc. J.A.K. received research grants from CareDx Inc., Sanofi-Genzyme, and CSL-Behringer. All other authors have no conflicts of interest to disclose.

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REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.
2. Kim IC, Youn JC, Kobashigawa JA. The past, present and future of heart transplantation. *Korean Circ J*. 2018;48(7):565-590.
3. Lee JH, Kim MS, Yoo BS, et al. KSHF Guidelines for the management of acute heart failure: part II. treatment of acute heart failure. *Korean Circ J*. 2019;49(1):22-45.
4. Kim K-J, Cho H-J, Kim M-S, et al. Focused update of 2016 Korean Society of Heart Failure Guidelines for the Management of Chronic Heart Failure. *Int J Heart Fail*. 2019;1(1):4-24.
5. Youn JC, Stehlik J, Wilk AR, et al. Temporal trends of de novo malignancy development after heart transplantation. *J Am Coll Cardiol*. 2018;71(1):40-49.
6. Choi HM, Park MS, Youn JC. Update on heart failure management and future directions. *Korean J Intern Med*. 2019;34(1):11-43.
7. Kim D, Choi JO, Oh J, et al. The Korean Organ Transplant Registry (KOTRY): second official adult heart transplant report. *Korean Circ J*. 2019;49(8):724-737.
8. Chang DH, Youn J-C, Dilibero D, Patel JK, Kobashigawa JA. Heart transplant immunosuppression strategies at cedars-sinai medical center. *Int J Heart Fail*. 2021;3(1):15-30.
9. Al-Adra DP, Hammel L, Roberts J, et al. Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement. *Am J Transplant*. 2021;21(2):460-474.
10. Kobashigawa J, Shah P, Joseph S, et al. Frailty in heart transplantation: Report from the heart workgroup of a consensus conference on frailty. *Am J Transplant*. 2021;21(2):636-644.
11. Oubari S, Naser E, Papathanasiou M, et al. Impact of time to diagnosis on Mayo stages, treatment outcome, and survival in patients with AL amyloidosis and cardiac involvement. *Eur J Haematol*. 2021;107(4):449-457.
12. Oechslin E, Kiowski W, Schneider J, Follath F, Turina M, Gallino A. Pretransplant malignancy in candidates and posttransplant malignancy in recipients of cardiac transplantation. *Ann Oncol*. 1996;7(10):1059-1063.
13. Sigurdardottir V, Bjortuft O, Eiskjaer H, et al. Long-term follow-up of lung and heart transplant recipients with pre-transplant malignancies. *J Heart Lung Transplant*. 2012;31(12):1276-1280.
14. Beaty CA, George TJ, Kilic A, Conte JV, Shah AS. Pre-transplant malignancy: an analysis of outcomes after thoracic organ transplantation. *J Heart Lung Transplant*. 2013;32(2):202-211.
15. Yoosabai A, Mehta A, Kang W, et al. Pretransplant malignancy as a risk factor for posttransplant malignancy after heart transplantation. *Transplantation*. 2015;99(2):345-350.
16. Delgado JF, Alonso-Pulpon L, Mirabet S, et al. Cancer incidence in heart transplant recipients with previous neoplasia history. *Am J Transplant*. 2016;16(5):1569-1578.
17. Wang YJ, Chiang TY, Hii IH, et al. Outcomes of heart transplant recipients with preexisting malignancies. *Transplant Proc*. 2018;50(9):2738-2741.
18. Youn JC, Chung WB, Ezekowitz JA, et al. Cardiovascular disease burden in adult patients with cancer: An 11-year nationwide population-based cohort study. *Int J Cardiol*. 2020;317:167-173.
19. Chung WB, Youn JC, Youn HJ. Cardiovascular complications of novel anti-cancer immunotherapy: old problems from new agents? *Korean Circ J*. 2020;50(9):743-753.
20. Stewart Coats AJ. Common co-morbidities in heart failure – diabetes, functional mitral regurgitation and sleep apnoea. *Int J Heart Fail*. 2019;1(1):25-41.
21. Kim I-C, Youn J-C, Lee SE, Jung S-H, Kim J-J. Donor heart utilization in Korea. *Int J Heart Fail*. 2020;2(4):254-263.
22. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant*. 2019;38(10):1056-1066.
23. Batra J, DeFilippis EM, Golob S, et al. Impact of pretransplant malignancy on heart transplantation outcomes: contemporary united network for organ sharing analysis amidst evolving cancer therapies. *Circ Heart Fail*. 2022;15(4):e008968.

24. Khush KK, Hsich E, Potena L, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-eighth adult heart transplantation report - 2021; focus on recipient characteristics. *J Heart Lung Transplant*. 2021;40(10):1035-1049.
25. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016;35(1):1-23.
26. Lim WH, Turner RM, Chapman JR, et al. Acute rejection, T-cell-depleting antibodies, and cancer after transplantation. *Transplantation*. 2014;97(8):817-825.
27. Ansari D, Lund LH, Stehlik J, et al. Induction with anti-thymocyte globulin in heart transplantation is associated with better long-term survival compared with basiliximab. *J Heart Lung Transplant*. 2015;34(10):1283-1291.
28. Rafiei M, Kittleson M, Patel J, et al. Anti-thymocyte gammaglobulin may prevent antibody production after heart transplantation. *Transplant Proc*. 2014;46(10):3570-3574.
29. Dillon TA, Sullivan M, Schatzlein MH, et al. Cardiac transplantation in patients with preexisting malignancies. *Transplantation*. 1991;52(1):82-85.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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