Received: 9 July 2019 | Revised: 17 November 2019 | Accepted: 25 November 2019

DOI: 10.1111/ctr.13762

ORIGINAL ARTICLE

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

Donor history of malignancy: A limited risk for heart transplant recipients

Sarah E. Rudasill[1] | Amit Iyengar[2] | Yas Sanaiha[1] | Habib Khoury[1] | Alexandra L. Mardock[1] | Sohail Sareh[1] | Peyman Benharash[1]

[1]Cardiovascular Outcomes Research Laboratories, David Geffen School of Medicine, University of California, Los Angeles, California

[2]Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

Correspondence
Peyman Benharash MD, Division of Cardiac Surgery, UCLA David Geffen School of Medicine, CHS 62-249, 10833 Le Conte Ave, Los Angeles, CA 90095.
Email: pbenharash@mednet.ucla.edu

Abstract

Organ donor contraindications are frequently reassessed for impact on recipient outcomes in attempt to meet demand for transplantation. This study retrospectively analyzed the United Network for Organ Sharing (UNOS) registry for adult heart transplants from 1987 to September 2016 to characterize the impact of donor malignancy history in heart transplantation. Kaplan-Meier estimates illustrated 10-year survival. Propensity score matching was utilized for 1:1 matching of donors with and without history of malignancy, and Cox proportional hazards and logistic regressions were used to analyze the matched population. Of 38 781 heart transplants, 622 (1.6%) had a donor history of malignancy. Cox regressions demonstrated that donor malignancy predicted increased 10-year mortality (HR = 1.16 [1.01-1.33]), but this difference did not persist when conditioned upon 1 year post-transplant survival (log-rank = 0.643). Cox regressions of the propensity score-matched population (455 pairs) found no association between donor malignancy and 10-year mortality (HR = 1.02 [0.84-1.24]). Older age and higher rates of hypertension were observed in donors with a history of malignancy whose recipients died within the first year post-transplant. Therefore, increased recipient mortality is likely due to donor characteristics beyond malignancy, creating the potential for expanded donor selection.

KEYWORDS

donor selection, heart transplantation, malignancy, mortality

1 | INTRODUCTION

The persistent gap between the demand for heart transplantation and supply of donor hearts has motivated reassessment of exclusion criteria for organ donation.[1,2] Donor selection strategies have increasingly allowed for transplantation of organs from donors with a history of malignancy.[3] While donors with primary central nervous system (CNS) malignancies have historically donated solid organs with minimal risk of malignant transmission to recipients, donors with a history of non-CNS malignancy have been generally classified as high-risk.[4,5]

Multiple studies have attempted to characterize the impact of prior donor malignancy, present in 2.2% of donors, on recipient outcomes across solid organ transplants.[6] Early analysis of the Israel Penn International Transplant Tumor Registry by Buell et al[3] found that among 296 cases of known or incidental donor malignancies, 42% had confirmed donor transmission. Subsequent case studies found that transmission rates between organ donor and recipient range from 0% to 42%, with aggressive malignancies—including breast cancer and melanoma—more likely to be transmitted than low-grade malignancies.[1,7-9] A more recent examination of all solid organ transplantations concluded that the risk of donor-origin cancers in transplant recipients was in fact minimal, with transmission as low as 0.06%.[10]

The US Donor Transmitted Assessment Committee and Council of Europe have provided scaled recommendations with regard to

donor malignancies but permit autonomous decision making with regard to transplant appropriateness.[5] However, in the absence of a national analysis of outcomes specific to heart transplantation, the true risk for donor transmission of malignancy remains uncharacterized.[1,11] Current selection guidelines for heart donors do not specify how to proceed with a donor history of malignancy.[12] Since post-transplant malignancy has emerged as one of the three leading causes of death following heart transplantation, evaluation of the impact of donor malignancy is critical to future decision making regarding organ allocation.[8] Therefore, this study examined the effect of donor history of malignancy on outcomes following heart transplantation in a national cohort.

2 | PATIENTS AND METHODS

This was a retrospective study of all adult patients undergoing heart transplantation in the United Network for Organ Sharing (UNOS) registry between 1987 and September 2016. Patients under the age of 18 and those with previous transplants and multi-organ transplants were excluded. Recipients were categorized based upon their donor's history of malignancy, while secondary stratification was by malignancy type and time period since last active malignancy. The primary outcome was 10-year mortality. Secondary outcomes included post-transplant dialysis, cerebrovascular accidents, extracorporeal membrane oxygenation (ECMO) at 72 hours, pacemaker implantation, rejection episodes within 1 year, acute rejection at 1 year, and cause of death.

The incidence of donor malignancies was evaluated across skin, central nervous system, genitourinary (GU), gastrointestinal (GI), breast, thyroid, leukemia/lymphoma, and other cancers. Ultimately, donor malignancies were stratified as CNS vs non-CNS, with further stratification by timeline, including groups for active malignancy within 1 year, malignancy within 1-5 years, malignancy >5 years, and unknown malignancy timeline. Continuous variables were compared using the Kruskal-Wallis test, and categorical variables were compared using chi-squared analysis. Survival analysis was performed via the Kaplan-Meier method with censoring at 10 years. An additional Kaplan-Meier model was conditioned upon 1-year recipient survival.

Given significant baseline differences between donors with and without a history of malignancy, we utilized the teffects psmatch function for 1:1 nearest neighbor propensity score matching of recipients with donor history of malignancy to those without a malignancy history. Characteristics significantly different at baseline were used to calculate propensity scores, which encompassed donor age, donor gender, donor race, donor body mass index (BMI), donor smoking history, donor diabetes, donor serum creatinine, donor history of hypertension, CDC high-risk blood-borne disease donor (deemed at high risk for transmission of human immunodeficiency virus (HIV) or hepatitis),[13,14] expanded criteria donor (aged 60 years or older, or over 50 years with at least two of the following conditions: hypertension history, serum creatinine >1.5 mg/dL, or cause of death from cerebrovascular accident),[15] donor cause of death, gender matching, recipient age, recipient gender, recipient history of malignancy, recipient insurance coverage, recipient cardiac output, and transplant year. Calipers were set at 0.372 in accordance with the standard recommendation of setting calipers at 0.2 multiplied by the standard deviation of the log of propensity scores. Propensity scores were checked for balance prior to generation of the sub-cohort of matched donors.

A Cox proportional hazards model was then utilized to analyze 10-year mortality in the propensity score-matched population. Logistic regression was used to evaluate the impact of donor malignancy on recipient post-transplant death from malignancy. Both analyses were then stratified by type of malignancy and malignancy timeline. In all comparisons, $P < .05$ was considered statistically significant. All statistical analyses were performed using STATA 14.2 (StataCorp LP).

3 | RESULTS

There were 38 781 heart transplants meeting inclusion criteria, of which 622 (1.6%) had a donor history of malignancy. The majority of malignancies were CNS (26.9%), followed by skin (21.7%) and genitourinary (17.7%), although the group for other cancers constituted 29.9% of the cohort (Table 1). In analysis by timeline, most malignancies had been inactive for >5 years (34.9%), with an unknown

TABLE 1 Donor malignancies by type and time before transplant

	Time before transplant				
Type of malignancy	**<1 y (N = 133)**	**1-5 y (N = 96)**	**5+ years (N = 217)**	**Unknown (N = 176)**	**Total (N = 622)**
Skin	35 (25.9%)	43 (31.9%)	33 (24.4%)	24 (17.8%)	135 (21.7%)
Central nervous system	53 (31.7%)	2 (1.2%)	14 (8.4%)	98 (58.7%)	167 (26.9%)
Genitourinary	9 (8.2%)	14 (12.7%)	77 (70.0%)	10 (9.1%)	110 (17.7%)
Gastrointestinal	0	2 (50.0%)	1 (25.0%)	1 (25.0%)	4 (0.6%)
Breast	0	1 (11.1%)	8 (88.9%)	0	9 (1.5%)
Thyroid	0	0	4 (100%)	0	4 (0.6%)
Leukemia/Lymphoma	0	0	7 (100%)	0	7 (1.1%)
Other	36 (19.4%)	34 (18.3%)	73 (39.2%)	43 (23.1%)	186 (29.9%)
Total	133 (21.4%)	96 (15.4%)	217 (34.9%)	176 (28.3%)	622

timeline for 28.3%, active malignancy <1 year for 21.4%, and remission of 1-5 years for 15.4% of donors.

As shown in Table 2, donors with a history of malignancy were older (42.2 vs 31.3 years, $P < .001$), less likely to be male (53.7% vs 70.7%, $P < .001$), and more likely to be Caucasian (86.7% vs 69.3%, $P < .001$). On average, donors with a history of malignancy also had an increased smoking history (28.1% vs 23.6%, $P = .009$), were more likely to fall under expanded donor criteria (10.3% vs 3.3%, $P = .001$), and had more frequent history of systemic hypertension (21.9% vs 12.9%, $P = .001$). Relative to recipients of hearts without donor malignancy, recipients of hearts with donor malignancy were on average older (55.0 vs 52.7 years, $P = .001$), less likely to be male (72.2% vs 75.7%, $P = .040$), and more likely to have a pre-transplant malignancy (8.5% vs 5.6%, $P = .001$). There was no difference in the use of preoperative life support, smoking history, or cardiomyopathy type between recipients of hearts with and without donor malignancy.

On univariate analysis of outcomes shown in Table 3, recipients of hearts with donor malignancy had increased rates of post-transplant dialysis (13.1% vs 8.8%, $P = .001$) but not increased rates of pacemaker use, cerebrovascular accidents, or rejection at 1 year. Ten-year survival was significantly reduced for recipients of a heart with a history of malignancy (Figure 1A, 51.6% vs 57.0%, $P = .002$). However, after application of 1-year conditional survival, this difference in 10-year mortality vanished (Figure 1B, log-rank $P = .643$). Univariate analysis by malignancy subtype demonstrated only non-CNS donor cancers to be associated with significantly greater mortality at 10 years (48.6% vs 57.0%, $P < .001$) relative to recipients of donors without a malignancy history. Analysis by malignancy timeline demonstrated donor cancers within 1-5 years (48.9% vs 57.0%, $P = .007$) and cancers with a history >5 years (53.0% vs 57.0%, $P = .004$) *both* yielded significantly greater mortality.

The distribution of balanced propensity scores by the presence of donor malignancy is shown in Figure 2, while analysis of the propensity score-matched cohorts can be found in Table 4. Cox proportional hazards modeling of the propensity-matched population demonstrated donor history of malignancy not to be a significant predictor of 10-year mortality (HR = 1.02 [0.84-1.24], $P = .814$). After stratification by donor malignancy type, neither CNS malignancy (HR = 0.85 [0.63-1.14], $P = .285$) nor non-CNS malignancies (HR = 1.09 [0.89-1.35], $P = .394$) were associated with greater 10-year mortality relative to recipients without a donor history of malignancy. Further stratification demonstrated that the timeline of donor malignancy was not associated with 10-year mortality. Similarly, donor malignancy was not a significant predictor of recipient death from post-transplant malignancy, even when analyzed by type or timeline.

Among recipients of hearts with donor history of malignancy, analysis was conducted between recipients who survived at least 1 year and those who did not (Table 5). Recipients with early death had a greater incidence of ischemic cardiomyopathy (45.9% vs 40.6%, $P = .003$) but otherwise did not differ in preoperative characteristics. However, donors for recipients dying within the first year were significantly older (46.3 vs 40.9 years, $P < .001$) and more likely to have a history of hypertension (31.2% vs 18.8%, $P = .003$). Malignancy was significantly more common as a cause of death in the early survival group relative to the early death group (13.1% vs 2.5%), while death from infection (7.4% vs 21.3%) and graft failure (1.7% vs 23.0%) was significantly more common in the early death group ($P < .001$). As shown in Table 6, those who faced death within 1 year had increased postoperative dialysis (40.2% vs 6.5%, $P < .001$) and increased death from graft failure (23.0% vs 0.6%, $P < .001$), infection (21.3% vs 2.8%, $P < .001$), and multi-organ failure (13.1% vs 2.8%, $P < .001$). Recipients of donor hearts with malignancies who faced early death did not have increased risk of cancer-specific mortality (2.5% vs 4.9%, $P = .241$).

4 | DISCUSSION

Since demand for heart transplantation exceeds organ availability, there is a growing focus on expanding organ donor criteria without sacrificing organ quality. The present study examined 38 781 patients to identify the impact of a history of donor malignancy on mortality following heart transplantation. Patients receiving a heart from donors with a history of malignancy were at increased risk of 10-year mortality, an effect that disappeared upon 1-year conditional survival. Propensity score matching indicates that this increased mortality risk is likely due to the overall suboptimal quality of the donor organ, especially given the absence of increased risk of post-transplant death directly attributable to malignancy.

The finding of increased mortality for recipients of hearts with donor history of malignancy is remarkable because it occurs within the first year of transplant. Propensity score matching illustrated that baseline differences, rather than a history of malignancy itself, were likely driving the increased early mortality. Furthermore, since recipients of donor malignancies who live >1 year only differ from those dying within 1 year in their diagnosed cardiomyopathy, donor characteristics are likely responsible. Donors with a history of malignancy whose recipients died within the first year were on average 6 years older than those whose recipients lived for >1 year. Increasing donor age has been associated with increased risk of mortality, perhaps as a result of increased chronic allograft vasculopathy and poorer cardiac function.[16,17] Donors also reported a greater history of systemic hypertension, which has been linked to postoperative complications and mortality.[18,19] It remains unclear whether these donor characteristics can be linked to their personal pre-transplant malignancy.

The significance of this finding is that donors with a history of malignancy may be appropriate for expansion of donor selection criteria to increase the pool of available hearts, particularly if additional donor comorbidities are minimized. While previous studies have found a small but significant cancer transmission risk from donor to recipient following solid organ transplantation, these have not focused specifically on heart transplants, which may carry a different risk of transmission than other solid organs.[1,4,10] Heart transplants may be relatively low risk for donor transmission given that the heart is an uncommon metastatic target, most likely due to the rarity of primary cancers, as well as differences in a malignancy's hematologic and lymphatic access and molecular profile.[20,21] While donor transmission of cancer presents a real risk,[1,5,7,8,10] our analysis

TABLE 2 Donor and recipient characteristics by the presence of donor malignancy

Variables	No donor malignancy (N = 38 159)	Donor malignancy (N = 622)	*P*
Donor characteristics			
Age (y)	31.3 ± 12.1	42.2 ± 11.6	<.001
Male	26 982 (70.7%)	334 (53.7%)	<.001
Race			<.001
White	26 430 (69.3%)	539 (86.7%)	
Black	5331 (14.0%)	36 (5.8%)	
Hispanic	5367 (14.1%)	36 (5.8%)	
Asian	572 (1.5%)	6 (1.0%)	
Other	450 (1.2%)	5 (0.8%)	
BUN (mg/dL)	16.2 ± 13.7	15.0 ± 10.1	.662
Creatinine (mg/dL)	1.3 ± 1.5	1.1 ± 0.94	.001
BMI (kg/m^2)	26.4 ± 5.5	27.1 ± 5.4	.001
Smoking history	9019 (23.6%)	175 (28.1%)	.009
Risk of a blood-borne pathogen	3112 (14.0%)	32 (9.1%)	.033
Alcohol use	3477 (15.7%)	60 (17.1%)	.450
Pulmonary infection	13 927 (36.5%)	220 (35.4%)	.562
Diabetes mellitus	969 (2.5%)	29 (4.7%)	.001
History of hypertension	4917 (12.9%)	136 (21.9%)	.001
Cause of death			.001
Anoxia	5588 (14.6%)	72 (11.6%)	
Cerebrovascular	9206 (24.1%)	230 (37.0%)	
Head trauma	22 483 (58.9%)	135 (21.7%)	
CNS tumor	170 (0.5%)	171 (2.3%)	
Other	711 (1.9%)	14 (2.3%)	
Recipient characteristics			
Age (y)	52.7 ± 12.0	55.0 ± 11.1	.001
Male	28 903 (75.7%)	449 (72.2%)	.040
Race			.617
White	27 862 (73.0%)	459 (73.8%)	
Black	6419 (16.8%)	95 (15.3%)	
Hispanic	2577 (6.8%)	41 (6.6%)	
Asian	908 (2.4%)	18 (2.9%)	
Other	393 (1.0%)	9 (1.5%)	
Cardiomyopathy			.341
Ischemic	16 816 (44.1%)	254 (40.9%)	
Restrictive	809 (2.1%)	19 (3.1%)	
Hypertrophic	698 (1.8%)	12 (1.9%)	
Dilated	17 355 (45.5%)	293 (47.2%)	
Other	2478 (6.5%)	43 (6.9%)	
Insurance			.002
Private	22 139 (58.0%)	343 (55.1%)	
Medicaid	4211 (11.0%)	48 (7.7%)	
Medicare	9850 (25.8%)	189 (30.4%)	
Other	1959 (5.1%)	42 (6.8%)	
BMI (kg/m^2)	26.6 ± 4.7	26.6 ± 4.8	.736

(Continues)

TABLE 2 (Continued)

Variables	No donor malignancy (N = 38 159)	Donor malignancy (N = 622)	*P*
Cardiac output (L/min)	4.5 ± 1.5	4.4 ± 1.4	.040
Previous cardiac surgery	16 265 (42.6%)	264 (42.4%)	.928
Ventricular assist device	11 008 (28.9%)	184 (29.6%)	.688
Smoking history	17 874 (46.8%)	289 (46.5%)	.851
Dialysis	1050 (2.8%)	11 (1.8%)	.136
Diabetes	8812 (23.1%)	152 (24.5%)	.414
Pre-transplant malignancy	2124 (5.6%)	53 (8.5%)	.001
Life support	27 311 (17.6%)	451 (72.5%)	.607
ECMO	150 (0.4%)	3 (0.5%)	.725
Wait time (d)	211 ± 338	216 ± 340	.764
Combined characteristics			
Donor/Recipient gender mismatch	10 509 (27.5%)	217 (34.9%)	.001
Donor/Recipient ABO mismatch	5656 (14.8%)	106 (17.0%)	.123
Donor/Recipient CMV mismatch	18 746 (49.3%)	311 (50.0%)	.743

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CMV, cytomegalovirus; CNS, central nervous system; ECMO, extracorporeal membrane oxygenation.

suggests that more attention should be placed on other donor markers of poor transplant outcomes, including increased donor age, expanded donor criteria, and history of hypertension.[12,22-24]

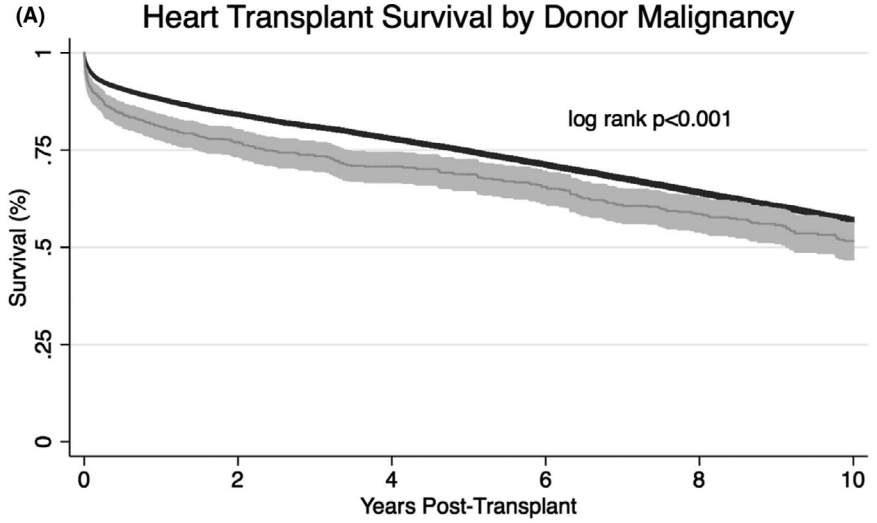
TABLE 3 Univariate outcomes by the presence of donor malignancy

Outcomes	No donor malignancy (N = 38 159)	Donor malignancy (N = 622)	*P*
Post-transplant dialysis	3318 (8.8%)	81 (13.1%)	.001
Pacemaker	1395 (3.7%)	32 (5.2%)	.119
CVA	949 (2.5%)	14 (2.3%)	.842
Rejection at 1 y	3810 (17.1%)	70 (19.9%)	.167
Cause of death			.573
Malignancy	1693 (10.8%)	26 (8.7%)	
Cardiovascular	2546 (16.2%)	47 (15.8%)	
Respiratory/BOS	526 (3.4%)	8 (2.7%)	
Other	10 936 (69.7%)	217 (72.8%)	
10-y survival			
Overall	57.0%	51.6%	.002
Timeline			
Cancer <1 y	57.0%	53.3%	.321
Cancer <5 y	57.0%	48.9%	.007
Cancer 5+ years	57.0%	53.0%	.004
Subtype			
CNS cancer	57.0%	59.1%	.746
Non-CNS cancer	57.0%	48.6%	<.001

Abbreviations: BOS, bronchiolitis obliterans syndrome; CNS, central nervous system; CVA, cerebrovascular accident.

Buell et al[3,25] first noted a transmission risk of 45% among just 22 cardiothoracic donors, and later analysis of 296 solid organ donors with a history of malignancy revealed a 42% cancer transmission risk. Yet in another study of 75 heart transplants from donors with a history of malignancy, pathologic examination revealed that none of the 8.8% of post-transplant recipient cancers were donor-derived.[6] Similarly, a study of 45 solid organ donors observed no donor-transmitted tumor among the recipients.[7] Despite small-scale studies indicating the possible use of donors with a history of malignancy, database analysis across solid organs has demonstrated that the risk of both donor-derived and donor-origin cancers is real.[10] The particular risk for hearts has been documented in a case report showing donor-derived metastatic prostate cancer in a heart transplant recipient.[26] More recent studies, however, have indicated that careful selection of donors with less invasive cancers has since reduced the overall risk of donor-derived cancer to an estimated 0.06%.[10,11]

Malignancy subtype and cancer-free period are additional considerations in donor selection criteria. Most malignancies in this analysis were skin and CNS cancers, followed by genitourinary and other cancers, which aligns with previous research findings.[1,7,8] In this study, no mortality difference was observed by malignancy type or timeline after propensity matching, most likely due to cautious selection of donors for less aggressive malignancies.[7] Current recommendations from the US Donor Transmission Advisory Committee risk stratify by malignancy type but are based upon studies of all solid organ transplantations and acknowledge the absence of strong evidence for transmission rates by organ.[5] Malignant melanoma, leukemia, and breast and colon cancers above stage 0 are deemed high risk and not appropriate for transplant except for "rare and extreme circumstances."[5] Other authors argue that melanoma remains an absolute contraindication, as a donor treated three decades before donation still transmitted melanoma to a lung transplant recipient.[27] Close attention to outcomes of recipients receiving an organ



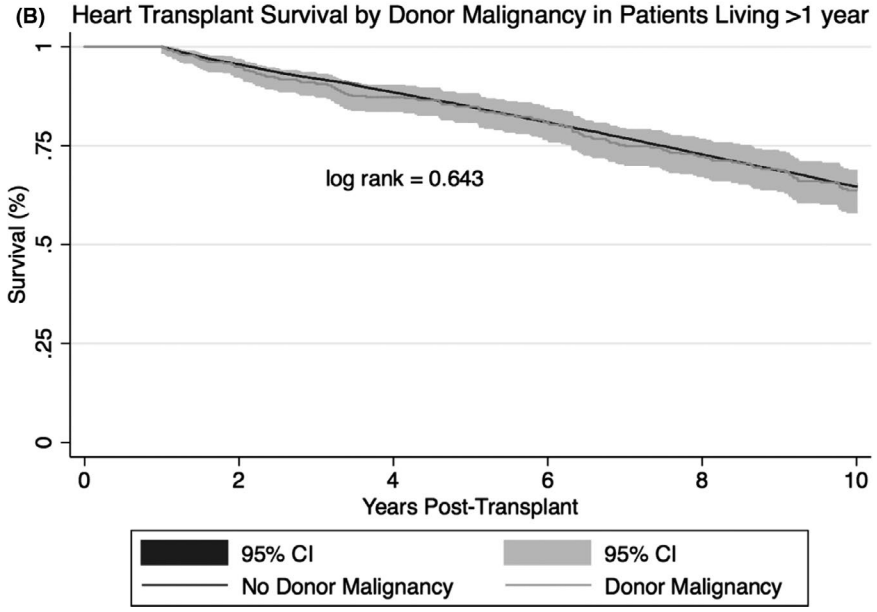


FIGURE 1 A, B, Heart transplant survival by donor malignancy. In figure A, heart transplant recipients of donors with a history of malignancy have increased 10-year mortality (log-rank $P < .001$). However, when Kaplan-Meier analysis is conditioned upon 1-year survival as in figure B, heart transplant recipients of donors with a history of malignancy have no difference in 10-year mortality (log-rank $P = .643$)

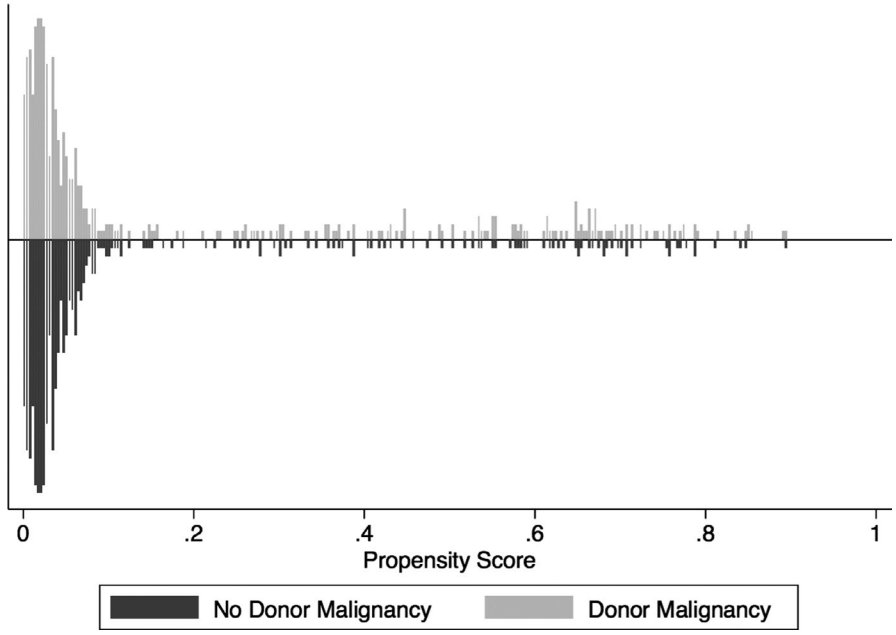


FIGURE 2 Propensity score matching using donor and recipient variables. Cox proportional hazards modeling on the 1:1 matched population found no significant impact of donor malignancy on 10-year mortality (HR = 1.02 [0.84-1.24], $P = .814$)

TABLE 4 Outcomes for propensity score-matched analysis

Risk factor	Ten-year mortality HR [95% CI]	*P*	Death from malignancy OR [95% CI]	*P*
Donor cancer	1.02 [0.84-1.24]	.814	0.89 [0.50-1.59]	.695
Type of cancer				
CNS cancer	0.85 [0.63-1.14]	.285	0.50 [0.17-1.48]	.210
Other cancer	1.09 [0.89-1.35]	.394	1.04 [0.57-1.90]	.907
Cancer timeline				
Cancer within 1 y	0.89 [0.66-1.21]	.456	0.83 [0.32-2.14]	.705
Cancer 1-5 y	1.04 [0.83-1.32]	.717	0.99 [0.49-2.02]	.984
Cancer 5+ years	0.97 [0.80-1.18]	.771	1.05 [0.58-1.89]	.877
Cancer unknown timeline	0.93 [0.72-1.19]	.558	0.74 [0.31-1.76]	.489

TABLE 5 Demographics and comorbidities of recipients of a donor malignancy with and without early death within 1 y post-transplant

Variables	No early death (N = 469)	Early death (N = 122)	*P*
Recipient characteristics			
Age (y)	54.7 ± 11.2	56.0 ± 10.3	.324
Male	344 (73.4%)	81 (66.4%)	.128
Cardiomyopathy			.003
Ischemic	190 (40.6%)	56 (45.9%)	
Restrictive	9 (1.9%)	10 (8.2%)	
Hypertrophic	10 (2.1%)	2 (1.6%)	
Dilated	227 (48.5%)	44 (36.1%)	
Other	32 (6.8%)	10 (8.2%)	
BMI (kg/m^2)	26.4 ± 4.7	27.2 ± 5.1	.197
Cardiac output (L/min)	4.4 ± 1.4	4.4 ± 1.4	.920
Previous cardiac surgery	192 (40.9%)	49 (40.2%)	.877
VAD	130 (27.7%)	33 (27.1%)	.883
Smoking history	221 (47.1%)	52 (42.6%)	.375
Dialysis	7 (1.5%)	4 (3.3%)	.193
Diabetes	117 (25.1%)	26 (21.3%)	.391
Pre-transplant malignancy	40 (8.5%)	11 (9.0%)	.864
Life support	330 (70.4%)	93 (76.2%)	.201
Cause of death			**<.001**
Graft failure	**3 (1.7%)**	**28 (23.0%)**	
Rejection	**12 (6.8%)**	**5 (4.1%)**	
Infection	**13 (7.4%)**	**26 (21.3%)**	
Cardiovascular	**30 (17.1%)**	**17 (13.9%)**	
Malignancy	**23 (13.1%)**	**3 (2.5%)**	
Multiple organ failure	**13 (7.4%)**	**16 (13.1%)**	
Other	**82 (46.6%)**	**27 (22.0%)**	
Donor characteristics			
Age (y)	40.9 ± 11.3	46.3 ± 11.3	<.001
Male	256 (54.6%)	58 (47.5%)	.165
BUN (mg/dL)	14.6 ± 9.5	15.0 ± 8.9	.610
Creatinine (mg/dL)	1.0 ± 0.9	1.0 ± 0.7	.794
BMI (kg/m^2)	27.0 ± 5.5	26.8 ± 4.8	.928

(Continues)

TABLE 5 (Continued)

Variables	No early death (N = 469)	Early death (N = 122)	*P*
Smoking history	131 (27.9%)	38 (31.2%)	.484
Expanded donor criteria	34 (7.3%)	25 (20.5%)	<.001
Risk blood-borne pathogen	24 (9.2%)	2 (3.5%)	.039
History of heavy alcohol consumption	42 (16.0%)	12 (21.1%)	.359
Pulmonary infection	161 (34.3%)	39 (32.0%)	.623
Diabetes mellitus	20 (4.3%)	7 (5.7%)	.488
History of hypertension	88 (18.8%)	38 (31.2%)	.003
Cause of death			.208
Anoxia	53 (11.3%)	8 (6.6%)	
Cerebrovascular	169 (36.0%)	53 (43.4%)	
Head trauma	97 (20.7%)	30 (24.6%)	
CNS tumor	140 (29.9%)	28 (23.0%)	
Other	10 (2.1%)	3 (2.5%)	
Combined characteristics			
Donor/Recipient gender mismatch	166 (35.4%)	41 (33.6%)	.712
Donor/Recipient ABO mismatch	75 (16.0%)	26 (21.3%)	.164
Donor/Recipient CMV mismatch	232 (49.5%)	63 (51.6%)	.411

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CMV, cytomegalovirus; CNS, central nervous system; VAD, ventricular assist device. The p value is listed in the row with cause of death because it's an ANOVA analysis among a group (<.001).

with a history of malignancy will be critical to better identifying specific transmission risks.

There are a number of limitations to this study. We are limited by the accuracy of data and potential coding errors within the UNOS database. This study also suffers from all limitations inherent to the retrospective multicenter design. United Network for Organ Sharing does not provide detailed data on donor cardiac function prior to transplant or recipient cardiac function post-transplant, which would have allowed for further analysis of differences between cohorts. We were also unable to ascertain whether malignant deaths were the result of de novo or donor-derived cancers, and we could not track the development of donor-derived malignancies that did not result in mortality. Furthermore, while we are able to track causes of death, including malignancy, infection, and multiple organ failure, we are unable to disentangle the underlying causes or ensure consistency in coding. In one study of 27 heart transplant recipients who developed a post-transplant malignancy, 21 patients (77.8%) died but only 10 had cancer as the recorded cause of death.[28] We cannot discern whether causes of death like infection and multiple organ failure occurred independently of a post-transplant malignancy or were secondary to treatment complications for malignancy. Future studies should explore opportunities for expansion of donor selection criteria given a history of malignancy and more closely examine present extended donor criteria for possible detrimental impact on recipient morbidity and mortality.

TABLE 6 Outcomes of recipients of a donor malignancy with and without early death within 1 y post-transplant

Outcomes	No early death (469)	Early death (122)	*P*
Post-transplant dialysis	30 (6.5%)	49 (40.2%)	<.001
Pacemaker	25 (5.4%)	6 (4.9%)	.074
Cerebrovascular accident	15 (3.2%)	9 (7.4%)	.020
Rejection at 1 y	53 (20.1%)	7 (12.3%)	.171
Cause of death			.005
Cardiovascular	30 (17.1%)	17 (13.9%)	.006
Respiratory	6 (3.4%)	2 (1.6%)	.759
Graft failure	3 (1.7%)	28 (23.0%)	<.001
Infection	13 (7.4%)	26 (21.3%)	<.001
Multiple organ failure	13 (7.4%)	16 (13.1%)	<.001
Malignancy	23 (4.9%)	3 (2.5%)	.241
Rejection	12 (2.6%)	5 (4.1%)	.365
Other	76 (43.2%)	25 (20.5%)	.262

As a result of these limitations, we suggest that it would be reasonable for a treatment team to conduct a careful evaluation of the risks and benefits of transplantation given a donor malignancy history, particularly when faced with a potential recipient in immediate medical need. Beyond considering the history of malignancy, the treatment team should give additional consideration for additional donor risk factors, as these issues may underlie differences in recipient morbidity and mortality.

In conclusion, transplant recipients receiving a heart from a donor with a history of malignancy faced increased 10-year mortality relative to recipients receiving hearts from donors without a cancer history. The increased mortality is almost entirely due to early mortality within the first year post-transplant. Propensity score matching eliminates the predictive effect of donor malignancy and suggests that differences in organ quality are responsible for the increased early mortality. We recommend that the treatment team carefully evaluate the risks and benefits of transplantation given a donor malignancy history, particularly when a potential recipient is in immediate medical need. Ultimately, efforts to expand donor selection criteria must consider the benefit of increased organ availability against the increased mortality associated with poorer quality organs. This study opens the possibility of expanding donor selection for those with a history of malignancy but suggests re-evaluating other elements of expanded donor criteria that may be drivers of early mortality.

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

ORCID

Amit Iyengar https://orcid.org/0000-0001-7689-1733

Peyman Benharash https://orcid.org/0000-0002-4705-0262

REFERENCES

1. Zhang S, Yuan J, Li W, Ye Q. Organ transplantation from donors (cadaveric or living) with a history of malignancy: review of the literature. *Transplant Rev*. 2014;28(4):169-175.
2. Ong L, Esmailian F, Conte AH. Pro: the benefits of utilizing expanded-criteria donors for orthotopic heart transplantation. *J Cardiothorac Vasc Anesth*. 2014;28(6):1686-1687.
3. Buell JF, Trofe J, Hanaway MJ, et al. Transmission of donor cancer into cardiothoracic transplant recipients. *Surgery*. 2001;130(4):660-668.
4. Watson CJE, Roberts R, Wright KA, et al. How safe is it to transplant organs from deceased donors with primary intracranial malignancy? An analysis of UK registry data: intracranial malignancy in UK organ donors. *Am J Transplant*. 2010;10(6):1437-1444.
5. Nalesnik MA, Woodle ES, DiMaio JM, et al. Donor-transmitted malignancies in organ transplantation: assessment of clinical risk: donor malignancy transmission risk assessment. *Am J Transplant*. 2011;11(6):1140-1147.
6. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Deceased donors with a past history of malignancy: an organ procurement and transplantation network/united network for organ sharing update. *Transplantation*. 2007;84(2):272-274.
7. Fiaschetti P, Pretagostini R, Stabile D, et al. The use of neoplastic donors to increase the donor pool. *Transplant Proc*. 2012;44(7):1848-1850.
8. Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. *Cold Spring Harb Perspect Med*. 2013;3(7):a015677-a015677.
9. Penn I. Transmission of cancer from organ donors. *Ann Transplant*. 1997;2(4):7-12.
10. Desai R, Collett D, Watson CJ, Johnson P, Evans T, Cancer NJ. Transmission from organ donors—unavoidable but low. *Risk: Transplant J*. 2012;94(12):1200-1207.
11. Doerfler A, Tillou X, Le Gal S, Desmonts A, Orczyk C, Bensadoun H. Prostate cancer in deceased organ donors: a review. *Transplant Rev*. 2014;28(1):1-5.
12. Kilic A, Emani S, Sai-Sudhakar CB, Higgins RSD, Whitson BA. Donor selection in heart transplantation. *J Thorac Dis*. 2014;6(8):1097-1104.
13. Tsiouris A, Wilson L, Sekar RB, Mangi AA, Yun JJ. Heart transplant outcomes in recipients of Centers for Disease Control (CDC) high risk donors. *J Card Surg*. 2016;31(12):772-777.
14. Iyengar A, Vucicevic D, Adams E, et al. Center for disease control high risk donor use in heart transplantation: current trends. *J Heart Lung Transplant*. 2017;36(4):S112-S113.
15. Rao PS, Ojo A. The alphabet soup of kidney transplantation: SCD, DCD, ECD–fundamentals for the practicing nephrologist. *Clin J Am Soc Nephrol*. 2009;4(11):1827-1831.
16. Weber DJ, Wang I, Gracon ASA, et al. The impact of donor age on survival after heart transplantation: an analysis of the United Network for Organ Sharing (UNOS) registry: donor age and outcomes in heart transplantation. *J Card Surg*. 2014;29(5):723-728.
17. Sorabella RA, Guglielmetti L, Kantor A, et al. Cardiac donor risk factors predictive of short-term heart transplant recipient mortality: an analysis of the united network for organ sharing database. *Transplant Proc*. 2015;47(10):2944-2951.
18. Smits JM, De Pauw M, de Vries E, et al. Donor scoring system for heart transplantation and the impact on patient survival. *J Heart Lung Transplant*. 2012;31(4):387-397.
19. Khush KK, Menza R, Nguyen J, Zaroff JG, Goldstein BA. Donor predictors of allograft use and recipient outcomes after heart transplantation. *Circ Heart Fail*. 2013;6(2):300-309.
20. Budczies J, von Winterfeld M, Klauschen F, et al. The landscape of metastatic progression patterns across major human cancers. *Oncotarget*. 2015;6(1):570-583.
21. Desai R. Donor transmitted and de novo cancer after liver transplantation. *World J Gastroenterol*. 2014;20(20):6170.
22. Carrier M, Lizé J-F. Impact of expanded-criteria donors on patient survival after heart, lung, liver and combined organ transplantation. *Transplant Proc*. 2012;44(7):2231-2234.
23. Coers Byram S, Ault L, Con M. The challenges of utilizing expanded-criteria donors for orthotopic heart transplantation. *J Cardiothorac Vasc Anesth*. 2014;28(6):1688-1690.
24. Rajagopalan N, Dennis DR, Ross HL, Tessmann P, Shafii A, Sekela ME. Utilizing expanded donor selection criteria for heart transplantation: a single center experience. *J Heart Lung Transplant*. 2017;36(4):S42-S43.
25. Buell JF, Beebe TM, Trofe J, et al. Donor transmitted malignancies. *Ann Transplant*. 2004;9(1):53-56.
26. Loh E. Development of donor-derived prostate cancer in a recipient following orthotopic heart transplantation. *JAMA J Am Med Assoc*. 1997;277(2):133.
27. Strauss DC, Thomas JM. Transmission of donor melanoma by organ transplantation. *Lancet Oncol*. 2010;11(8):790-796.
28. Wang Y-J, Chi N-H, Chou N-K, et al. Low incidence of malignancy after heart transplantation in Taiwan. *Transplant Proc*. 2016;48(3):974-977.

How to cite this article: Rudasill SE, Iyengar A, Sanaiha Y, et al. Donor history of malignancy: A limited risk for heart transplant recipients. *Clin Transplant*. 2020;34:e13762. https://doi.org/10.1111/ctr.13762