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Effect of Peripheral Vascular Disease on Mortality in Cardiac Transplant Recipients (from the United Network of Organ Sharing Database)

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Abstract

Peripheral vascular disease (PVD) portends increased morbidity and mortality in patients with heart failure. In those with advanced heart failure, heart transplantation (HT) is the only causative therapy to increase survival. However, little is known about the impact of symptomatic PVD on survival of HT recipients in large multicenter cohorts. The aim of this study was to investigate an association between recipient symptomatic PVD and survival after HT. We analyzed 20,297 patients from the United Network of Organ Sharing data set. Survival analysis using a control cohort established by propensity matching was performed. There was an increased prevalence of traditional cardiovascular risk factors in 711 patients with symptomatic PVD compared with 19,586 patients without PVD. Patients with pre-transplant symptomatic PVD had increased post-transplant mortality compared with those without PVD (1-, 5- and 10-year survival rate 91.5% vs 94.9%, 74.8% vs 82.6%, 48.6% vs 54.7%, respectively, log-rank $p < 0.001$). On multivariate analysis based on the propensity matching, factors associated with a lower survival rate were presence of PVD (hazard ratio 1.20, 95% confidential interval 1.02 to 1.42, $p = 0.030$), and female gender (hazard ratio 1.22, 95% confidence interval 1.02 to 1.47, $p = 0.034$). In conclusion, patients with symptomatic PVD have a lower survival rate after HT. Symptomatic PVD should be considered an independent risk factor for poor prognosis in patients undergoing HT evaluation.

Heart transplantation (HT) is the only causative treatment for patients with advanced heart failure (HF). However, because of the scarcity of donors, selection of appropriate candidates

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has become more rigorous. The screening methods for candidacy include evaluation for peripheral vascular disease (PVD) when warranted, and in those candidates with moderate-to-severe PVD, HT is contraindicated in 30% of US transplant centers.¹ Furthermore, because of the longevity of HT recipients, there is still a concern for patients with HF and PVD to develop accelerated and new-onset atherosclerosis after HT. Previous studies have shown a 10% incidence of developing an accelerated form of atherosclerosis leading to PVD after HT.² Additionally, the role of immunosuppression (i.e., prednisone, cyclosporine) may enhance metabolic abnormalities such as hyperlipidemia that may further advance atherosclerotic vascular disease. Earlier studies have shown that the presence of PVD is a risk factor for death from any cause after cardiac transplantation.³ Because of the paucity of data on the impact of survival in HT recipients with PVD, we sought to analyze the United Network of Organ Sharing (UNOS) database to examine the association between symptomatic PVD in patients with advanced HF and survival after HT.

Methods

Standard transplant analysis and research files with followup were obtained from the UNOS database. These data included all heart transplant recipients and donors in the United States and reported to the Organ Procurement and Transplantation Network from 1990 to 2010. There is one record per waiting list registration/transplantation event, and another record includes the most recent follow-up information (including patient and graft survival) reported to the Organ Procurement and Transplantation Network as of the date the file was created. To ensure the confidentiality of centers and patients, the data set does not include any patient or transplant center identifiers except for a unique patient identification number. Follow-up data are represented as 1 record per follow-up per transplantation event. Some patients have multiple records in a given year, whereas others have only 1 record. Patients lost to follow-up were censored at the time of last known follow-up. The Institutional Review Board of Columbia University Medical Center approved the present study.

Patients selected were of age ≥ 18 years undergoing first-time HT from 1990 to 2010 ($n = 20,297$). PVD was defined as the presence or absence of symptomatic PVD (yes or no) based on the UNOS Heart Transplant Recipient Registration Form. Thus, patients were stratified according to the presence or absence of symptomatic PVD and were excluded if they underwent other simultaneous organ transplantation or if demographical, diagnostic, or follow-up data were missing. Patients were monitored from the date of transplantation to 2010, which was the last day of follow-up provided by UNOS. Baseline characteristics including age, gender, body mass index, cause of HF, and renal and liver function parameters were collected.

Continuous variables are reported as mean $\pm$ SD, and comparison was carried out with the Student t test. Categorical variables are reported as percentages, and comparison was done with the chi-square test. The outcome of interest was death after transplantation. The patients who were alive at the last follow-up were censored. The survival is presented with Kaplan-Meier plots and was compared with the log-rank test. In addition, median survival time was estimated along with its 95% confidence interval. The univariate and multivariate Cox proportional hazards regression analyses were carried out to assess the risk of PVD on

survival. In addition, analysis was carried out using propensity score. The propensity score was calculated with a multivariate logistic regression model on the PVD status with the adjustment of following factors: age, gender, race/ethnicity, cause of HF (ischemic or nonischemic), hypertension, diabetes, dialysis, previous stroke, creatinine level, and total bilirubin. Then, 3 adjusted Cox proportional hazards models were fitted: one with 2 covariates (PVD and continuous propensity score), one with 3 covariates (PVD, gender, and continuous propensity score), the other with covariates identified in the analysis of total cohort. Furthermore, conditional logistic regression analysis was carried out with 5:1 ratio of propensity score matching. For all statistical analyses, a 2-tailed $p < 0.05$ was considered significant. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina). Propensity score matching is done by “radius” matching with an allowable absolute difference 0.01 between exact propensity scores with an SAS macro on matching propensity score at 5:1 ratio.

Results

The demographic and clinical characteristics before matching and the balance achieved after matching are summarized in Tables 1 and 2, respectively. The study population included 20,297 adult recipients from the UNOS data registry. Of these, 711 (3.5%) had symptomatic PVD and 19,586 (96.5%) did not have symptomatic PVD. After matching for significant imbalances in patient characteristics, patients in the PVD group compared with the no PVD group were mostly Caucasians and more frequently have a smoking history (Table 2).

Multivariate analysis in the entire data set demonstrated that the presence of PVD, black race, hypertension, diabetes mellitus, and dialysis at registration were independent factors associated with increase mortality in HT recipients (Table 3). After propensity analysis, only the presence of PVD and female gender were independent predictors of mortality (Table 4).

Kaplan-Meier survival analysis revealed that the survival rate for the PVD versus no PVD group was 91.5% versus 94.9% at 1 year, 74.8 % versus 82.6% at 5 years, and 48.6% versus 54.7% at 10 years, respectively (log-rank $p < 0.001$; Figure 1). After propensity analysis, there was still a lower survival rate in the PVD group compared with that in the no PVD group (Figure 1).

Discussion

Findings from our study demonstrate a strong association between the presence of symptomatic PVD and the burden of risk factors for development of atherosclerosis (hypertension, dyslipidemia, diabetes, smoking, renal dysfunction, and stroke). HF of ischemic origin was strongly associated with PVD suggesting a systemic atherosclerotic process in this cohort. On multivariate analysis, the presence of cardiovascular risk factors such as symptomatic PVD, diabetes, and dialysis at registration were shown to be independent predictors of worse survival in HT recipients. The significant association of symptomatic PVD with increased mortality after propensity score analysis suggests that the impact of PVD was independent of the measured baseline characteristics that include key cardiovascular risk factors.

Strong associations between PVD and hard outcomes are probably due to an interaction of confounding variables such as age, coronary artery disease, diabetes, and hypertension. However, previous studies have shown PVD as an independent predictor of mortality in patients with advanced HF. Jones et al⁴ demonstrated that patients with PVD and a decrease in baseline functional capacity were older (median age 67 years), actively smoking, had ischemic cardiomyopathy, diabetes, hypertension, myocardial infarction, and stroke. After controlling for these confounding variables, the presence of PVD remained an independent predictor for all-cause mortality and hospitalization. More recently, in a well-balanced propensity-matched population of patients with chronic HF with a history of PVD, there was a 40% increase for all-cause mortality after risk adjustment for traditional cardiovascular risk factors.⁵ Similar to and expanding these studies, we observed after propensity analysis that the presence of symptomatic PVD remained a predictor for mortality in HT recipients. One likely explanation for these clinical outcomes is the presence of diffuse and advanced atherosclerotic disease in patients with PVD, which can further progress after HT.^{6,7} This progress might be associated with declining exercise capacity to avoid claudication and an increased morbidity and mortality.^{8,9}

Despite advances in the treatment of HT recipients, there is still a major concern for progression of atherosclerotic disease, which can lead to significant morbidity and mortality. Previous studies have shown that HT recipients develop vascular disease within 3 years after HT, with 1/2 of them showing accelerated atherosclerosis including abdominal aortic aneurysms and aortoiliac disease.^{10–12} Using the UK national study database, Ganesh et al reported that PVD is a risk factor for early (<30 days) post-HT mortality.¹³ More recently, however, this finding has been challenged in small cohort studies that did not reveal an association between recipient PVD and post-transplant survival.¹⁴

Our study, to our knowledge, is the first revealing the impact of PVD on post-HT clinical outcomes using a large multicenter cohort of patients from the UNOS database. Russo et al¹⁵ had analyzed the pretransplant characteristics of recipients and survival after combined heart-kidney transplantation. Among the risk factors associated with worse survival, a history of PVD was found to have a fourfold risk. Consistent with those findings and even after multivariate analysis and balancing for confounding variables, the presence of symptomatic PVD was a strong predictor of mortality after HT in our analysis. A possible explanation for the differences in post-HT survival seen in our analysis could be the persistence of cardiovascular risk factors and systemic atherosclerosis in ischemic cardiomyopathy recipients. Previous investigations have shown that patients with ischemic cardiomyopathy undergoing HT have a significant presence of PVD and have a lower long-term survival rate compared with those with idiopathic cardiomyopathy, which could be related to the existence of cardiovascular risk factors that produced the cardiomyopathy originally.^{16–18} This cardiovascular risk profile of ischemic cardiomyopathy transplant recipients might be associated with the overall vascular function after HT. Previous investigations have demonstrated that HT recipients with previous ischemic cardiomyopathy have a blunted vascular function during the first year after HT because of continued endothelial dysfunction and oxidative stress, which can lead to decrease long-term survival.^{19–21} This plausible mechanism could explain the decrease in the survival rate seen

in the PVD group as early as 1 year after transplantation, which persisted to decrease throughout the course of the study.

Our study is limited by being a retrospective analysis of the UNOS database and the data available to us. In our study using a large cohort of patients, it was unlikely to be affected by missing data. However, it is known that registries have variability in data entry, which can affect analysis and interpretation of the results. More importantly, the UNOS reporting system defines PVD only as symptomatic PVD, but this criterion varies by center, and there is no category to determine the degree of severity based on functionality or need for revascularization procedures. Additionally, only 3.5% of the entire cohort had symptomatic PVD, which is lower compared with the incidence reported by others.^{9,22} This is noticeable in the group categorized as no PVD in which a greater proportion of patients had ischemic heart disease as the cause of their HF. It is possible that PVD may have been underdiagnosed in those with pre-existing symptomatic PVD who underwent revascularization procedures.

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Figure 1.

(A) Kaplan-Meier survival curves of patients with and without PVD. The *Blue line* indicates patients with PVD, and the *red line* indicates patients without PVD. (B) Kaplan-Meier survival curves of patients (propensity cohort) with and without PVD. The *Blue line* indicates patients with PVD, and the *red line* indicates patients without PVD.

Table 1

Baseline clinical characteristics (entire cohort)

Variables	Peripheral Vascular Disease		p-Value
	Yes (n = 711)	No (n = 19,586)	
Age (years)	56.4 ± 8.0	51.7 ± 11.8	<0.001
Male (n, %)	591 (83.1%)	14941 (76.3%)	<.0001
White	604 (85.0%)	15166 (77.4%)	<.0001
Black	72 (10.1%)	2702 (13.8%)	
Hispanic	27 (3.8%)	1216 (6.2%)	
Other	8 (1.1%)	502 (2.6%)	
Etiology			<.0001
Ischemic	529 (74.4%)	9143 (46.7%)	
Non-ischemic	131 (18.4%)	8169 (41.7%)	
Other	51 (7.2%)	2274 (11.6%)	
Body mass index (kg/m ²)	26.6 ± 4.8	26.3 ± 5.1	0.176
Hypertension	381 (53.6%)	7352 (37.5%)	<.0001
Diabetes mellitus	270 (38.0%)	3713 (19.0%)	<.0001
Smoker	95 (13.4%)	1874 (9.6%)	<.0001
Dialysis at registration	17 (2.4%)	262 (1.3%)	0.018
Stroke	114 (16.0%)	1048 (5.4%)	<.0001
Creatinine (mg/dL)	1.49 ± 0.9	1.39 ± 1.2	0.004
Total bilirubin (mg/dL)	1.21 ± 2.1	1.35 ± 3.2	0.098
Albumin (g/dL)	3.72 ± 0.8	3.65 ± 0.8	0.108

Table 2

Baseline clinical characteristics (propensity cohort)

Variables	Peripheral Vascular Disease		p-Value
	Yes (n = 711)	No (n = 3,526)	
Age (years)	56.4 ± 8.0	56.5 ± 10.3	0.598
Male (n, %)	591 (83.1%)	2959 (84.5%)	0.362
White	604 (85.0%)	2914 (82.6%)	<.0001
Black	72 (10.1%)	276 (7.8%)	
Hispanic	27 (3.8%)	194 (5.5%)	
Other	8 (1.1%)	142 (4.0%)	
Etiology			<.0001
Ischemic	529 (74.4%)	2931 (83.1%)	
Non-ischemic	131 (18.4%)	416 (11.8%)	
Other	51 (7.2%)	179 (5.1%)	
Body mass index (kg/m ²)	26.6 ± 4.8	26.8 ± 5.1	0.428
Hypertension	381 (53.6%)	1944 (55.8%)	0.521
Diabetes mellitus	270 (38.0%)	1526 (43.4%)	0.011
Smoker	95 (13.4%)	416 (11.8%)	0.002
Dialysis at registration	17 (2.4%)	97 (2.8%)	0.594
Stroke	114 (16.0%)	579 (16.4%)	0.829
Creatinine (mg/dL)	1.49 ± 0.9	1.49 ± 1.6	0.960
Total bilirubin (mg/dL)	1.21 ± 2.1	1.23 ± 2.5	0.813
Albumin (g/dL)	3.72 ± 0.8	3.63 ± 0.8	0.039

Table 3

Univariate and multivariate Cox proportional hazards models on mortality after heart transplantation based on entire cohort

Variable	Univariate		Multivariate	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
PVD (yes = 1, no = 0)	1.26 (1.11–1.44)	0.0003	1.16 (1.01–1.33)	0.033
Age (year-old)	1.00 (0.99–1.00)	0.483		
Gender (female = 1, male = 0)	1.06 (1.00–1.12)	0.036	1.06 (0.99–1.13)	0.059
White (reference)	1		1	
Black	1.18 (1.10–1.27)	<0.0001	1.18 (1.09–1.27)	<0.0001
Hispanic	1.07 (0.97–1.19)	0.187	1.06 (0.95–1.18)	0.329
Other	1.21 (1.05–1.41)	0.011	1.21 (1.02–1.43)	0.027
Etiology (ischemic = 1, non-ischemic = 0)	1.05 (0.99–1.10)	0.064	1.05 (0.99–1.11)	0.093
Hypertension (yes = 1, no = 0)	1.10 (1.05–1.16)	<0.0001	1.07 (1.02–1.13)	0.012
Diabetes mellitus (yes = 1, no = 0)	1.22 (1.15–1.30)	<0.0001	1.23 (1.15–1.31)	<0.0001
Smoker (yes = 1, no = 0)	0.99 (0.86–1.15)	0.929		
Dialysis at registration (yes = 1, no = 0)	1.42 (1.16–1.73)	0.0006	1.28 (1.01–1.61)	0.042
Stroke (yes = 1, no = 0)	1.12 (1.01–1.24)	0.028	1.10 (0.99–1.23)	0.090
Creatinine (mg/dL)	1.01 (0.99–1.03)	0.096	1.01 (0.99–1.02)	0.457
Total bilirubin (mg/dL)	0.99 (0.99–1.01)	0.654		
Albumin (mg/dL)	1.01 (0.96–1.05)	0.810		

Table 4

Univariate and multivariate conditional logistic regression models on mortality after heart transplantation based on the propensity cohort

Variable	Univariate		Multivariate	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
PVD (yes = 1, no = 0)	1.20 (1.02–1.42)	0.033	1.20 (1.02–1.42)	0.030
Age (year-old)	1.00 (0.99–1.01)	0.817		
Gender (female = 1, male = 0)	1.22 (1.01–1.46)	0.037	1.22 (1.02–1.47)	0.034
White (reference)	1	0.210		
Black	0.96 (0.74–1.24)	0.755		
Hispanic	1.42 (0.99–2.01)	0.051		
Others	1.94 (0.71–5.33)	0.199		
Etiology (ischemic = 1, non-ischemic = 0)	0.82 (0.60–1.11)	0.194		
Hypertension (yes = 1, no = 0)	0.92 (0.78–1.08)	0.311		
Diabetes mellitus (yes = 1, no = 0)	1.05 (0.88–1.26)	0.588		
Smoker (yes = 1, no = 0)	1.02 (0.47–2.22)	0.968		
Dialysis at registration (yes = 1, no = 0)	1.36 (0.92–2.02)	0.129		
Stroke (yes = 1, no = 0)	1.01 (0.78–1.32)	0.929		
Creatinine (mg/dL)	1.01 (0.97–1.05)	0.778		
Total bilirubin (mg/dL)	0.99 (0.97–1.02)	0.590		
Albumin (mg/dL)	1.02 (0.87–1.18)	0.828		