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RESEARCH ARTICLE

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Persistence of pulmonary hypertension in patients undergoing ventricular assist devices and orthotopic heart transplantation

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Abstract

Pulmonary hypertension (PH) is common in advanced heart failure and often improves quickly after left ventricular assist device (VAD) implantation or orthotopic heart transplantation (OHT), but long-term effects and outcomes are not well-described. This study evaluated PH persistence after VAD as destination therapy (VAD-DT), bridge to transplant (VAD-OHT), or OHT-alone. The study constituted a retrospective review of patients who underwent VAD-DT ($n = 164$), VAD-OHT ($n = 111$), or OHT-alone ($n = 138$) at a single tertiary-care center. Right heart catheterization (RHC) data was collected pre-, post-intervention (VAD and/or OHT), and 1-year from final intervention (latest-RHC) to evaluate the longitudinal hemodynamic course of right ventricular function and pulmonary vasculature. PH (Group II and Group I) definitions were adapted from expert guidelines. All groups showed significant improvements in mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure (PAWP), cardiac output, and pulmonary vascular resistance

Abbreviations: Cpc-PH, combined postcapillary pulmonary hypertension; HF, heart failure; IpcPH, isolated postcapillary pulmonary hypertension; LV, left ventricle; OHT, orthotopic heart transplantation; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension in the setting of left heart disease (group 2 PH); PreCPH, precapillary pulmonary hypertension (group 1 pulmonary hypertension); RV, right ventricle.

(PVR) at each RHC with greatest improvement at post-intervention RHC (post-VAD or post-OHT). PH was reduced from 98% to 26% in VAD-OHT, 92%−49% in VAD-DT, and 76%−28% in OHT-alone from preintervention to latest-RHC. At latest-RHC mPAP remained elevated in all groups despite normalization of PAWP and PVR. VAD-supported patients exhibited suppressed pulmonary artery pulsatility index (PaPi < 3.7) with improvement only posttransplant at latest-RHC. Posttransplant patients with PH at latest-RHC ($n = 60$) exhibited lower survival (HR: 2.1 [95% CI: 1.3−3.4], $p < 0.001$). Despite an overall significant improvement in pulmonary pressures and PH proportion, a notable subset of patients exhibited PH post-intervention. Post-intervention PH was associated with lower posttransplant survival.

KEYWORDS

orthotopic heart transplantation, pulmonary hypertension, right ventricular function, ventricular assist devices

INTRODUCTION

Heart failure (HF) affects more than six million people in the United States with a projected increase in prevalence by 46% in the next two decades.[1] Pulmonary hypertension (PH) is common in HF in left heart disease (PH-LHD, Group II PH) with a reported prevalence ranging from 54% to 83% in HF with preserved ejection fraction (HFpEF)[2,3] and 73% in HF with reduced ejection fraction (HFrEF).[4] Previous studies have reported an increased 30-day posttransplant mortality associated with right ventricular (RV) failure in chronic HF patients with pretransplant PH.[5,6] Patients with end-stage HF who develop PH exhibit refractory symptoms despite optimized medical therapy and may require specialized intervention such as orthotopic heart transplantation (OHT) or mechanical circulatory devices (MCD). Despite notable improvements in the prevention and treatment of HF-related risk factors and tailored medical therapy,[1,7] PH-LHD patients still comprise a stratum with high risk of mortality and hospitalization.[2,8–10]

Although rates of heart transplantation have steadily increased over the last decade, the number of patients with advanced HF (New York Heart Classification III−V, NYHA) remains significantly greater than the number of available donor hearts[11]; subsequently, ventricular assist devices (VADs) emerged as an important therapeutic modality in advanced HF with >20,000 implantations over the last two decades.[12] VADs are MCDs that augment left ventricular (LV) function by improving cardiac output (CO) in patients with HFrEF and are used as destination therapy (DT) or bridge to cardiac transplantation in patients evaluated for OHT. VADs improve RV and pulmonary pressures in the short and intermediate term (30−180 days) in PH-LHD, however, studies with longitudinal hemodynamic data are small, with a primary focus on reversal of elevated pulmonary vascular resistance (PVR; given increased likelihood of postoperative RV failure).[13–15] VADs have improved survival in chronic HF,[12,16] however, RV failure still negatively impacts survival in VAD-assisted patients.[17] Importantly, VAD-OHT patients who experienced decreased survival at 1-year posttransplant had higher mean pulmonary artery pressure (mPAP) and PVR compared to OHT-alone.[18] Therefore, patients managed with VADs may exhibit chronic PH-LHD albeit with lower RV and pulmonary pressures, possibly contributing to higher morbidity and mortality. The paucity of long-term hemodynamic data with respect to PH-LHD in patients post-OHT limits evaluation of RV adaptation to chronic pressure overload (i.e., HF) required to characterize PH persistence. Thus, we sought to evaluate the prevalence and the natural hemodynamic course of PH and RV function in patients receiving VAD and/or OHT to provide further insight into long-term effects of persistent PH.

METHODS

This study is a retrospective analysis of 413 patients with advanced HF who underwent evaluation and received intervention from 2008 to 2021 for OHT and/or VAD at University of Pittsburgh Medical Center. Designation of VAD as bridge to transplant (VAD-OHT), VAD as DT (VAD-DT), or orthotopic heart transplant alone

(OHT-alone) was determined based on review of medical records of treatment received by the patient by two independent reviewers (A. R. and A. E.-S.). This study was approved by the Institutional Review Board at the University of Pittsburgh (STUDY20090170). Baseline demographics, comorbidities, and laboratory data were collected within 1 month of first right heart catheterization (RHC) before initial intervention ("preintervention") defined as RHC before VAD or OHT. Hemodynamic data from RHC were obtained within a median of 30 ± 7 days before intervention, 3 ± 1 months post-intervention (post-VAD in VAD-DT or post-OHT in OHT alone, and after each intervention in VAD-OHT), and 12 ± 4 months after last intervention (latest-RHC in VAD or OHT). Survival was evaluated in patients 1-year from cardiac transplant till at the end of the retrospective study period designated as February 1, 2021.

Evaluation of invasive hemodynamics

HF was categorized by LV ejection fraction (LVEF) with HFrEF defined as EF ≤40% by echocardiography. PH definitions were adapted from 2018 World Congress on PH guidelines[19] and derived from RHCs at rest in the supine position. Patients with Group III–V PH were not present in the study given as OHT and/or VAD are not standard of care and group-specific treatment modalities are recommended.[20] Precapillary PH (PreCPH, or Group I PH) was defined as mPAP >20 mmHg, pulmonary artery wedge pressure (PAWP) < 15 mmHg & PVR ≥3 wood unit (WU). PH-LHD (Group II PH) was defined as mPAP >20 mmHg & PAWP ≥15 mmHg and further subcategorized into isolated postcapillary PH (IpcPH) defined by PVR < 3 WU and combined postcapillary PH (CpcPH) defined by PVR >3 WU. Isolated elevated mPAP was defined as mPAP ≥20 mmHg, PAWP < 15 mmHg and PVR < 3 WU, and normal hemodynamics (i.e., no PH) defined as mPAP <20 mmg, PAWP < 15 mmHg, and PVR < 3 WU (Supporting Information: Figure 1). We defined total PH (or PH) burden in this study to include both PreCPH & PH-LHD emphasizing total PH burden with concomitant end-stage HF. RHC measures including mPAP, PAWP, right atrial pressure (RAP), CO (by thermodilution), pulmonary artery systolic pressure (PASP), pulmonary artery diastolic pressure (PADP), and heart rate were obtained to calculate pulmonary artery pulsatility index (PAPi, calculated as PASP-PADP/RAP), pulmonary artery elastance (PA Ea, calculated as PASP/stroke volume [SV]), pulmonary artery compliance (PAC, calculated as SV/pulmonary artery pulse pressure, the latter defined as PASP-PADP), and PVR (calculated as mPAP-PAWP/CO). PAPi <3.7 was defined as the threshold for abnormal RV function based on previous studies.[21–23]

Statistical analyses

Data are expressed as mean with standard deviation for normally distributed continuous variables or median with interquartile range for skewed continuous variables, and absolute value with percent for categorical variables. Comparison of variables between treatment groups used Students *t*-test or one-way analysis of variance (with Welch's *t*-test) for continuous variables, Mann–Whitney *U* test or Kruskal–Wallis test for skewed continuous variables, and χ^2 test or Fisher's exact test for categorical variables where appropriate. Generalized linear models using the generalized estimating equation (GEE) was utilized to evaluate differences in repeated measures of hemodynamic variables and proportion of PH within each treatment group and utilized the Wald test to evaluate statistical significance. GEE with auto-regression working correlation matrices was used to reflect the correlation among the outcomes over the different time periods (RHC in longitudinal order). Comparisons among time periods (RHC order) were conducted using the Bonferroni correction for multiplicity. Complete cases were used for the primary analysis. Imputation was considered but not pursued owing to the longitudinal focus of our study and avoiding overestimation of hemodynamic values and proportions similar to previous studies.[24] Kaplan–Meier method was used to estimate univariate unadjusted survival curves in patients with and without PH 1 year from OHT and the log-rank test was used to compare among survival curves. Cox proportional-hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) between groups. Proportional hazards assumption was assessed using Schoenfeld residual plots. Data management and analysis were performed using SPSS Version 27.0 (IBM Corp.) and R statistical package (version 4.0.2; R Core Team, 2022). Figures and illustrations were produced using Prism 9 (GraphPad Software), Biorender (Biorender.com), and the R statistical package. *p*-value < 0.05 was considered statistically significant.

RESULTS

A total of 413 patients were evaluated for VAD and OHT during the study period: 111 patients underwent VAD-OHT, 164 VAD-DT, and 138 had OHT-alone. Overall, patients were predominantly male (78%), Caucasian (81%) with no significant differences in comorbidities

(Table 1 and Supporting Information: Table 1), and all were classified as NYHA class IIIb–IV. Significant differences in age were observed in VAD-OHT patients as they received VAD and OHT relatively younger than VAD-DT or OHT-alone patients. OHT-alone patients had the lowest BMI relative to VAD-DT and VAD-OHT (Table 1). Significant differences in baseline laboratory values were present, with higher total bilirubin in VAD-DT, higher creatinine in VAD-OHT, and lower MELD scores in OHT-alone, with marginally higher sodium levels in OHT-alone (Supporting Information: Table 2).

Presence of PH at preintervention RHC was high in all groups: 98% in VAD-OHT, 92% in VAD-DT, and 76% in OHT-alone (Figure 1). At preintervention, presence of PreCPH was <5% in all treatment groups (Supporting Information: Figure 2A-C). Independent of treatment received, there was an overall significant reduction in the proportion of PH during the period of study (Figure 1). VAD-OHT patients exhibited reduction of PH from 98% at preintervention to 48% at post-VAD RHC; however, at post-OHT and latest-RHC, a trend toward further reduction in PH was observed but was not statistically significant (Figure 1). PH in VAD-DT improved to 68% at post-VAD with a nonsignificant reduction to 49% at latest-RHC. OHT-alone patients showed significant reduction in PH at each RHC and 28% had PH at

TABLE 1 Baseline demographics.

		VAD-OHT ($N = 111$)	VAD-DT ($N = 164$)	OHT-alone ($N = 138$)	p Value
Age at VAD	-	51 (14)	58 (13)	-	0.001
Age at OHT	-	52 (14)	-	55 (12)	0.042
BMI	-	29 (6)	30 (6)	27 (4)[a]	0.001
Caucasian	81% (333/412)	85% (93/110)	73% (120/164)	87% (120/138)	0.005
Elixhauser index	-	8 (7)	8 (6)	7 (6)	0.699
Male (%)	78% (321/412)	83% (89/110)	76% (130/164)	74% (102/138)	0.362

Note: Values are expressed in mean (SD) or percentage. p Value is derived by ANOVA with Welch's T-test, Krusal–Wallis, or Student's t-test used for continuous variables and χ^2 test used for categorical variables. $p < 0.05$ is considered statistically significant. Analyses for multiple comparisons were adjusted using the Bonferroni or Games–Howell method.

Abbreviations: BMI, body mass index; OHT, orthotopic heart transplant; SD, standard deviation; VAD, ventricular assist device; VAD-DT, VAD as destination therapy.

[a]VAD-DT or VAD-OHT versus OHT-alone. Elixhauser index: composite score of comorbid disease severity based on the international classification of disease (ICD).

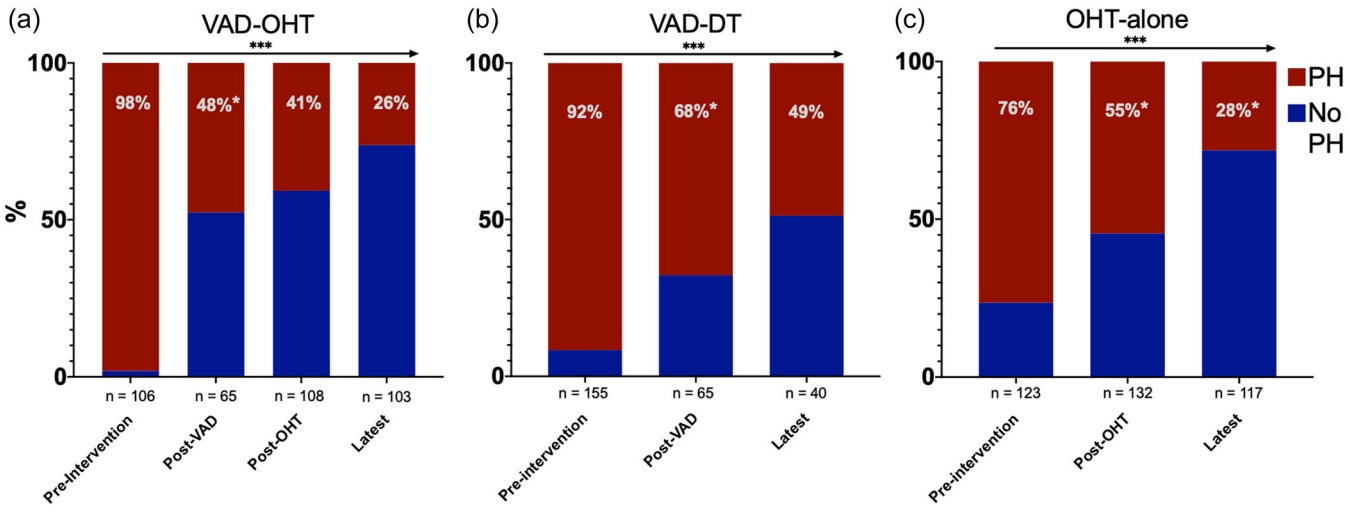

FIGURE 1 Prevalence of pulmonary hypertension (PH) on RHC on pre- and post-intervention VAD as bridge to transplant (VAD-OHT, a), destination therapy (VAD-DT, b), and orthotopic transplant only (OHT-alone, c). Panel arrow denotes linear reduction in the proportion of PH at successive RHC by treatment group with statistical significance ***$p < 0.001$ by the generalized estimating equation utilizing the Wald test. * denotes within group comparison (current bar compared to previous bar) by the Bonferroni method. p Values < 0.05 was considered statistically significant. OHT, orthotopic heart transplantation; RHC, right heart catheterization; VAD, ventricular assist device.

latest-RHC. The predominant hemodynamic subphenotypes of PH at preintervention in VAD-OHT were equally IpcPH and CpCH at 48% and 46%, respectively (Supporting Information: Figure 2A), with similar observations in VAD-DT (44% with IpcPH and CpcPH, Supporting Information: Figure 2B). However, in OHT-alone, 50% of patients had IpcPH while 22% had CpcPH (Supporting Information: Figure 2C). At latest-RHC, IpcPH was present at 19% in VAD-OHT and 17% in OHT-alone with no CpcPH in VAD-OHT and 1% in OHT-alone (Supporting Information: Figure 2A,C). VAD-DT exhibited the highest proportion of patients with persisting IpcPH and CpcPH at 33% and 18%, respectively (Supporting Information: Figure 2B). However, a notable degree of missing data was present at post-VAD RHC in VAD-OHT and VAD-DT (Supporting Information: Table 5) which can bias proportion of PH and its subtypes and is discussed in detail below under limitations in the discussion section.

Hemodynamic evaluation of RV function throughout the study showed significant reduction in all measured variables in all groups with exception of PAPi in VAD-DT (Table 2). Patients who underwent VAD-OHT had significant reductions in pulmonary pressures overall but exhibited abnormal mPAP, PAWP, RAP, and PaPi related to treatment received at specific RHCs (Figure 2a and Table 2). Elevated mPAP and RAP were observed despite PVR < 3 WU and normal PAWP at post-VAD and post-OHT in VAD-OHT. A nonsignificant improvement in mPAP, PAWP, CO, and RAP at post-OHT despite successive improvement in PVR was observed. Significant improvement in mPAP, RAP, and PAWP were observed at latest-RHC, and specifically in PAPi which was suppressed (<3.7) at previous RHCs (Table 2). PA Ea and PAC significantly improved post-VAD and PA Ea at latest-RHC independent of PVR. However, at latest-RHC a notable proportion of patients exhibited elevated mPAP and RAP with suppressed PaPi (Figure 2a and Table 3).

Despite improvements, patients undergoing VAD-DT had elevated mPAP with borderline elevation of PAWP post-VAD despite reduction of PVR (Table 2). No additional reductions in pulmonary pressures were noted at latest-RHC except RAP, which nonetheless remained abnormally elevated. PaPi in the VAD-DT group did not improve throughout the study despite significant improvements in PA Ea and PAC post-VAD which remained unchanged till latest-RHC; this is further highlighted by the distribution and proportion of abnormal values of key hemodynamic variables at each RHC in VAD-DT (Figure 2b). At latest-RHC, VAD-DT exhibited a large proportion of abnormal mPAP, PAWP, RAP, and PAPi (Figure 2b and Table 3).

Patients undergoing OHT-alone had the lowest overall preintervention pulmonary pressures and RV-specific parameters (Table 2). This group had continued improvement in all measures at successive RHC except RAP which only normalized in a majority of patients at latest-RHC. Like VAD-OHT, post-OHT mPAP surprisingly remained slightly elevated with borderline elevated PAWP despite improved PVR. Notably, the OHT-alone group had the lowest PVR overall at preintervention. PaPi was reduced post-OHT with improved CO in the postsurgical setting associated with unchanged RAP which persisted until latest-RHC. Distribution of key hemodynamic variables at each RHC exhibited a notable proportion of patients with abnormal values despite an improvement in averaged pressures (Figure 2c and Table 3). At latest-RHC, mPAP was elevated in 49% of patients and reduced PAPi persisted in 39% similar to 45% in VAD-OHT (Table 3). PA Ea and PAC showed continued improvement at each RHC in the setting of PVR < 3 WU (Table 2).

At 1-year post-OHT (latest-RHC in VAD-OHT and OHT-alone), a total of 60 patients exhibited PH on RHC. These patients exhibited reduced survival compared to patients with no hemodynamically defined PH (no PH; Figure 3, HR: 2.1 [95% CI: 1.3−3.4], $p < 0.001$). Median survival probability was 96% (CI: 92%−99%) in the no PH group and 90% (83%−98%) in the PH group at 1-year and was 69% (61%−78%) and 46% (33%−62%), respectively at 10-years from latest-RHC. We did not observe mortality at 1-year post-intervention (time of latest-RHC) in patients exhibiting PreCPH during the study period (Supporting Information: Figure 3), limiting the possibility of an effect of early PreCPH-associated mortality on survival in this cohort. Multivariate Cox proportional hazard modeling was performed to evaluate the impact of age, BMI, and previous VAD implantation on the PH presence on survival. These covariates were chosen as they were statistically significant between VAD-OHT and OHT-alone groups. BMI was statistically significant albeit with a small effect on survival (HR: 1.05, 95% CI: 1.0−1.20, $p < 0.01$), but age or previous VAD-implantation were not significant risk factors and violated assumptions of the Cox proportional hazards model. Univariate analysis of the presence of PH on survival had a HR of 2.13 (95% CI: 1.3−3.4) and the multivariate analysis of presence of PH and BMI survival had a HR of 2.18 (95% CI: 1.32−3.61) with both being statistically significant ($p < 0.001$). At 10-years from latest-RHC, 47% (CI: 34%−65%) of patients with elevated PAWP (≥15 mmHg, Supporting Information:Figure 4) survived compared to 68% (CI: 61%−78%) with normal PAWP; a similar survival estimate was observed in patients with PH-LHD (PreCPH excluded) where 46%

TABLE 2 Longitudinal right heart catheterization-based hemodynamics by treatment groups.

	(A) VAD-OHT					(B) VAD-DT				(C) OHT-alone			
	Preintervention	Post-VAD	Post-OHT	Latest	*p* Value	Preintervention	Post-VAD	Latest	*p* Value	Preintervention	Post-OHT	Latest	*p* Value
mPAP (mmHg)	41 (8)	26 (9)[a]	24 (6)	21 (6)[d]	0.001	38 (10)	29 (10)[a]	27 (10)	0.001	31 (11)	25 (7.0)[b]	21 (5.0)[d]	0.001
PAWP (mmHg)	28 (8)	14 (8)[a]	14 (5)	12 (6)[d]	0.001	26 (8)	15 (7)[a]	15 (7)	0.001	21 (9)	15 (5.0)[b]	12 (5.0)[d]	0.001
RAP (mmHg)	13 (7)	10 (6)[a]	9 (4)	6 (4)[d]	0.001	13 (7)	12 (7)	10 (6)[c]	0.002	9 (6)	9 (5)	5 (4)[d]	0.001
CO (L/m)	4.4 (1.5)	5.5 (1.3)[a]	6.1 (1.5)	6.1 (1.4)	0.001	4.4 (1.3)	5.6 (1.5)[a]	5.4 (1.5)	0.001	4.5 (1.2)	5.9 (1.4)[b]	5.9 (1.3)	0.001
PVR (WU)	3.1 (1.6)	2.4 (1.2)[a]	1.7 (0.6)[b]	1.6 (0.8)	0.001	3.1 (1.5)	2.7 (1.5)[a]	2.3 (1.4)	0.001	2.5 (1.2)	1.7 (0.6)[b]	1.6 (0.7)	0.001
PA Ea (mmHg/mL)	1.2 (0.5)	0.7 (0.3)[a]	0.6 (0.2)	0.5 (0.2)[d]	0.001	1.1 (0.5)	0.7 (0.3)[a]	0.7 (0.4)	0.001	0.9 (0.4)	0.6 (0.2)[b]	0.5 (0.2)[d]	0.001
PAC (mL/mmHg)	1.8 (1.2)	2.8 (1.0)[a]	3.1 (1.6)	4.0 (1.5)	0.001	2.1 (1.6)	2.7 (1.2)[a]	2.9 (1.3)	0.002	2.6 (1.6)	2.8 (1.0)[b]	3.8 (1.3)[d]	0.001
PAPi	3.1 (2.1)	3.0 (1.7)	3.2 (1.7)	4.2 (2.2)[d]	0.001	3.0 (2.2)	2.8 (2.0)	3.2 (2)	0.641	4.0 (2.3)	3.1 (1.5)[b]	4.6 (2.4)[d]	0.001

Note: *p* value <0.05 is considered statistically significant. Values expressed as mean (SD). *p* Value signifies overall statistical differences between groups using the Wald χ^2 test by the generalized estimating equation model. Post hoc analysis using Bonferroni correction for significance between groups.

Abbreviations: CO, cardiac output by thermodilution; mPAP, mean PA pressure; OHT, orthotopic heart transplantation; PA, pulmonary artery; PAC, PA capacitance; PA Ea, PA elastance; PAPi, PA pulsatility index; PAWP, PA wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SD, standard deviation; VAD, ventricular assist device; VAD-DT, VAD as destination therapy; WU, woods unit.

[a]Pre- versus post-VAD.

[b]Post-VAD versus post-OHT.

[c]Post-VAD versus latest.

[d]Post-OHT versus latest-RHC.

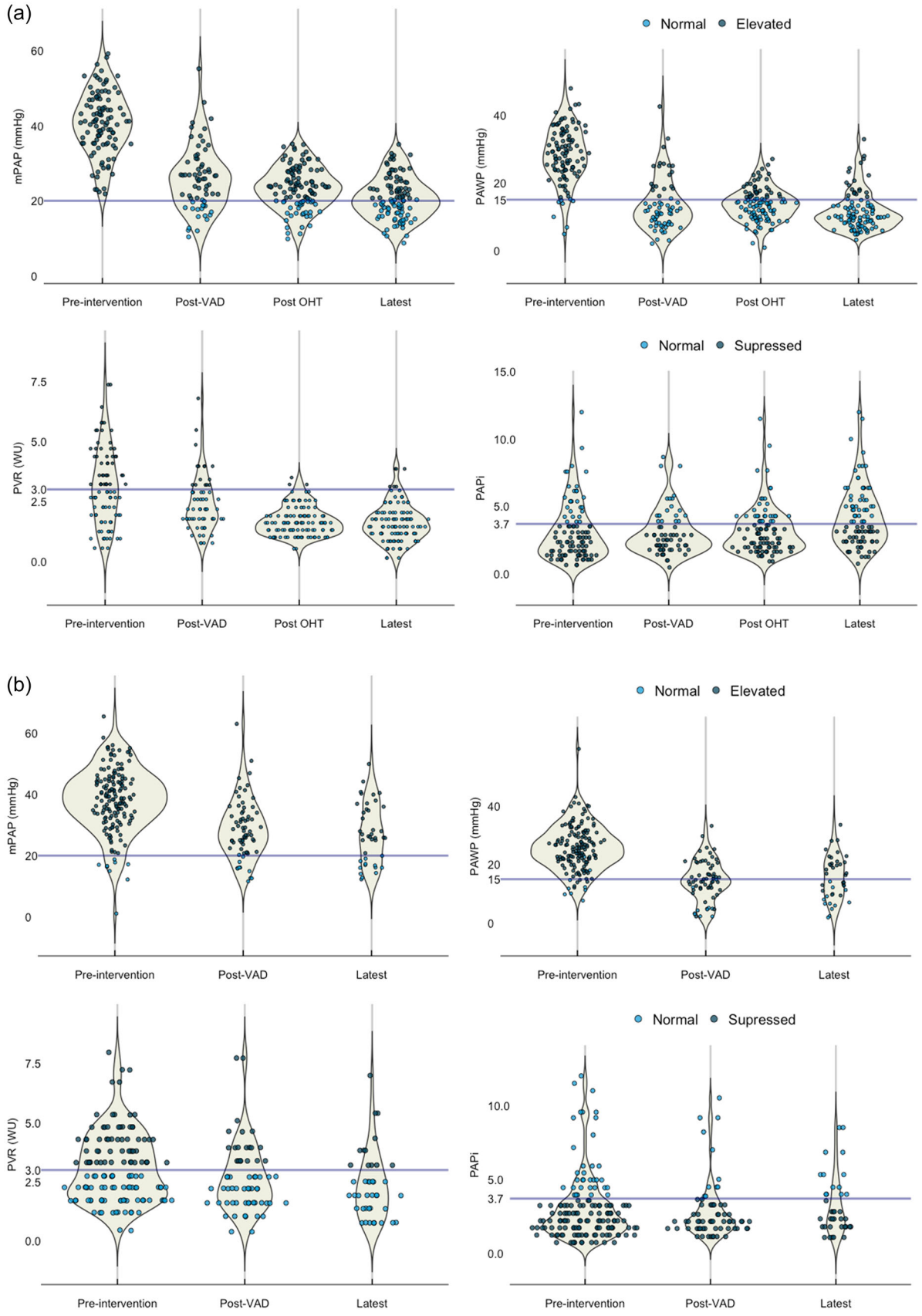

FIGURE 2 (Continued).

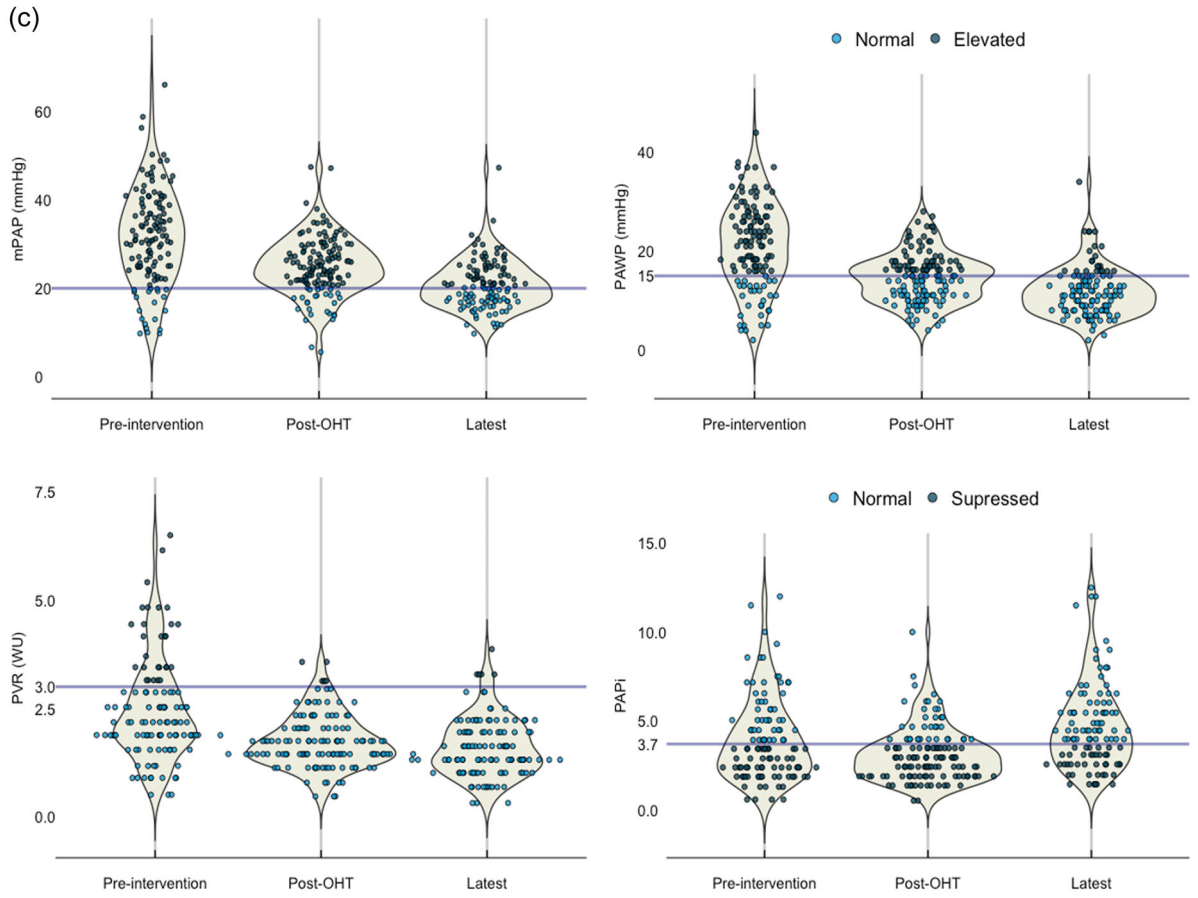

FIGURE 2 (a) Distribution and proportion of patients with normal versus abnormal measures in selected hemodynamic variables in the VAD-OHT group. Consistent reduction in key hemodynamic measures were observed during the study period with a notable number of patients with abnormal values at latest-RHC (abnormal mPAP and PaPi despite improved PAWP and PVR). Blue line signifies cut-off values delineating normal versus abnormal or normal versus suppressed in PaPi. (b) Distribution and proportion of patients with normal versus abnormal measures in selected hemodynamic variables in the VAD-DT group. Consistent reduction in key hemodynamic measures were observed during the study period with a notable number of patients with abnormal values at latest-RHC (abnormal mPAP and PaPi despite improved PAWP and PVR). Blue line signifies cut-off values delineating normal versus abnormal or normal versus suppressed in PaPi. (c) Distribution and proportion of patients with normal versus abnormal measures in selected hemodynamic variables in the OHT-alone group. Consistent reduction in key hemodynamic measures were observed during the study period with a notable number of patients with abnormal values at latest-RHC (abnormal mPAP and PaPi despite improved PAWP and PVR). Blue line signifies cut-off values delineating normal versus abnormal or normal versus suppressed in PaPi. mPAP, mean pulmonary artery pressure; OHT, orthotopic heart transplantation; PAPi, pulmonary artery pulsatility index; PAWP, pulmonary artery wedge pressure; PVR, peripheral vascular resistance; RHC, right heart catheterization; VAD, ventricular assist device; VAD-DT, VAD as destination therapy.

(CI: 33%–64%) of patients survived relative to 69% (CI: 61%–78%) of patients with no PH-LHD at 10 years.

DISCUSSION

In a cohort of patients with advanced HF who underwent VAD, OHT, or both we demonstrate persistence of PH despite longitudinal improvements in hemodynamics and identified IpcPH as the predominant subtype in all groups after intervention. Additionally, we observe VAD-OHT patients show additive improvements in pulmonary pressures after OHT and complete amelioration of CpcPH in all post-OHT patients. We observe that despite expected normalization of LVEF (Supporting Information: Figure 5) and reduced PAWP at latest-RHC in most post-OHT patients, a significant proportion still had abnormal mPAP, RAP, and PAPi (Figure 2a–c and Table 3). Finally, we observe PH persistence in a subset of patients at 1-year posttransplant (from both VAD-OHT and OHT-alone cohorts) which was associated with an increased risk of mortality with 50% of

patients surviving at 9.5 years compared to 64% without posttransplant PH.

The RV is a thin walled, crescent shaped, and low-pressure conduit system which is embryologically[25] and physiologically different from the LV.[26] The RVs adaptation to pressure and volume remains tightly coupled to the pulmonary vasculature to maintain optimal cardiac function in normal and disease states, including PH,[27] requiring RHC data to diagnose PH and evaluate RV function. PH persistence after advanced intervention (VAD or OHT) in end-stage HF remains an important area of study given its impact on adaptive and maladaptive RV responses which affect survival and morbidity.[28] However, heterogeneity in PH definitions used,[14,19,29] updated expert definitions of PH-LHD, and variable sample sizes with longitudinal hemodynamic data has limited the evaluation of PH persistence. Within our entire cohort, at preintervention CpcPH and IpcPH was prevalent in 37% and 47% of all patients, respectively; by latest-RHC, IpcPH persisted in 17%–33% of all patients dependent on the treatment group, whereas CpcPH comparatively resolved in post-OHT patients (CpcPH reduced to 18% in VAD-DT patients). Resolution of CpcPH post-OHT in VAD-OHT and OHT-alone groups was likely secondary to selection of patients with PVRs <5WU to reduce likelihood of postoperative early and late RV failure.[11,30] Patients who underwent VAD-DT were near equivalent to VAD-OHT in terms of pulmonary hemodynamics and baseline demographics at preintervention and likewise showed reduced PH burden

TABLE 3 **Hemodynamics at latest-RHC with proportion of patients with abnormal measures.**

	VAD-OHT ($n = 101$) (%)	VAD-DT ($n = 41$) (%)	OHT-alone ($n = 115$)(%)
mPAP (mmHg)	48	68	49
PAWP (mmHg)	19	49	19
RAP (mmHg)	39	71	27
PAPi	45	65	39
PVR (WU)	6	29	4

Note: Percent of patients with abnormalities in key hemodynamic variables at latest-RHC across treatment groups. Values are reported as percentage of patients above or below cut-off for mPAP >20 mmHg, PAWP >15 mmHg, PVR <3 WU, RAP >6 mmHg, and PaPi <3.7.

Abbreviations: mPAP, mean pulmonary artery pressure; OHT, orthotopic heart transplantation; PaPi, pulmonary artery pulsatility index; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; VAD, ventricular assist device; VAD-DT, VAD as destination therapy; WU, woods unit.

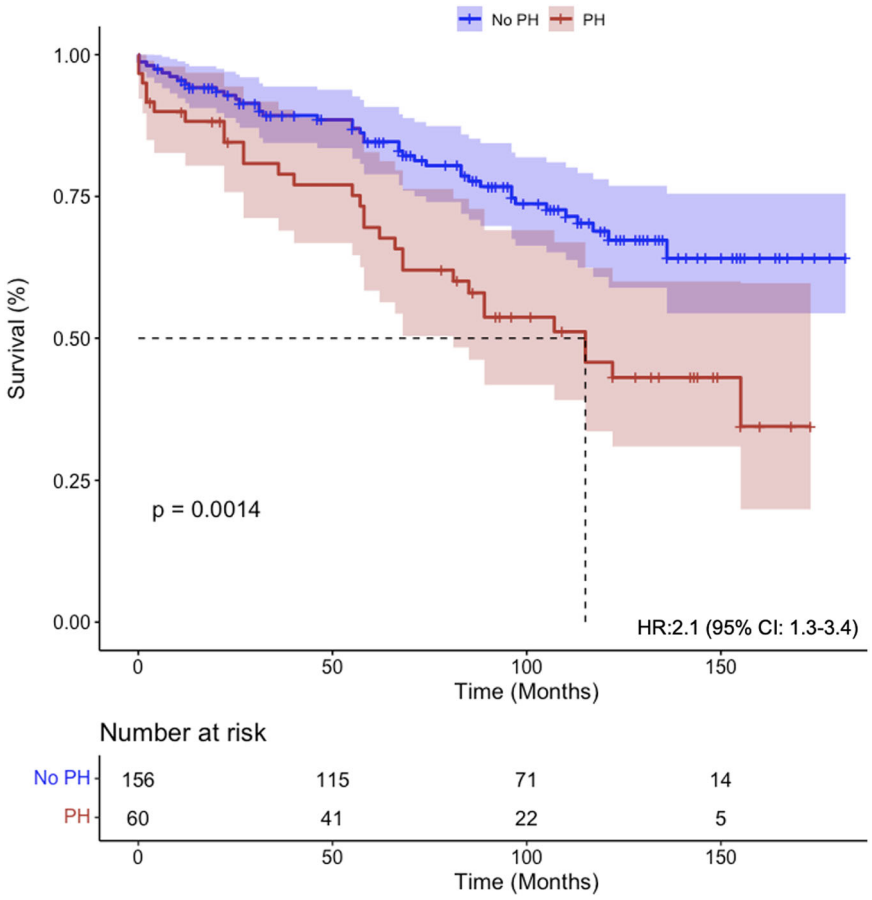

FIGURE 3 Kaplan–Meier curves in posttransplant patients with and without PH. Unadjusted survival analysis of patients with PH (total PH) versus no PH shows significant differences in survival over the 14-year study period. Hazard ratio (HR) is derived using the Cox proportional hazards method with *p*-value using the log-rank test. PH, pulmonary hypertension.

cumulatively albeit with higher proportions of IpcPH and CpcPH at latest-RHC; presence of PH in VAD-DT may potentially be related to duration of PH-LHD (advanced age) and confounding with VAD-related mortality (120/164 by latest-RHC, Supporting Information: Table 3). The proportion of IpcPH as the predominant phenotype was unexpected but may suggest underlying chronic RV remodeling in HF without significant pulmonary remodeling (PVR < 3WU). Patients defined as PreCPH by RHC (Supporting Information: Figure 2A-C) at preintervention were most likely true PAH ($n = 8$ across all VAD-OHT, VAD-DT, and OHT-alone groups) with hemodynamic and clinical assessment confirming this for four patients and one patient known to have received heart-lung transplant. The majority received VAD support ($n = 7/8$) likely due to cardiac decompensation. However, patients defined as PreCPH at latest-RHC ($n = 13$) could have been CpcPH patients subjected to therapeutics that may attenuate PAWP (i.e., aggressive diuresis), and therefore this subset of 13 patients requires careful interpretation bearing in mind this possibility.

RV function is sensitive to changes in afterload in acute and chronic pressure overload when compared to LV in HF.[31] Therefore, any improvement in vascular resistance in the pulmonary circulation by VAD should translate to improved RV function. In our cohort, post-VAD RV dysfunction (RVD) is characterized by increased mPAP, RAP, and suppressed PaPi (<3.7)[23] despite effective VAD-related unloading. PaPi is a surrogate measure of RV function and useful in VAD patients given VAD mechanically augments LV function.[32] In our cohort, PaPi does not change during VAD support, suggestive of RVD, and significant improvement (>4.0) is only observed 1-year after transplant (latest-RHC). Furthermore, patients with elevated mPAP post-intervention may be at continued, increased risk of mortality, morbidity, and progression of PH likened to studies evaluating patients with "borderline" or "high-risk" PH.[33] Effective LV unloading is further demonstrated by improvements in PA Ea and PAC which are corollary measures of RV afterload alongside PVR which hemodynamically describe the dynamic (pulsatile) and static (resistive) forces of pulmonary resistance which independently impact survival in PH.[34,35] Altogether, we observe a significant improvement consistent with reversal of the pulmonary vascular adaptation independent of intervention in a majority proportion of patients; in conjunction, reductions in mPAP, PAWP, and RAP at post-VAD & post-OHT are observed, but these measures have not altogether normalized in a notable proportion of patients (Table 3) suggestive of RVD especially in the latest-RHC setting. Together, these findings highlight the limited reversal of RV adaptation consistent with persistent PH observed within the entire cohort and previously in post-VAD patients[31,36] despite improvements in pulmonary vascular compliance (PVR, PAC).

Patients having undergone OHT-alone exhibited lower burden of PH at pre- and latest-RHC and showed notable improvements in successive RHCs. Nonetheless, at latest-RHC in both OHT-alone and VAD-OHT groups, despite improved pulmonary pressures 1-year postcardiac transplant, a notable proportion of patients had abnormal RHC measures (Figure 2c and Table 3) with an average of 26%−28% with persistent PH; these patients had a twofold increase in hazard over a 14-year study period. The post-OHT patients without PH likely exhibit a 14-year median survival time comparative to the posttransplant national average.[16] Juxtaposed against PH-LHD who had 7.5-year median survival, the impact of PH persistence on survival within this cohort appears to be strongly related to PAWP (Supporting Information: Figure 4). The presence of posttransplant PH, specifically IpcPH, is likely due to a combination of factors such as cardiac donor characteristics, underlying RVD, maladaptation of pulmonary vasculature not evident by RHC, hidden chronic transplant rejection related changes, or possibly consequences of donor-recipient pulmonary artery anastomoses mismatch secondary to surgery. Further studies are needed to investigate mechanisms impacting reduced survival in post-OHT patients with persistent PH.

Our study has several limitations. First, the single center retrospective nature of the study limits causal inference on the relationship between RVD and PH persistence given heterogeneity of treatment received in VAD and OHT patients and the variable number of repeated RHCs per treatment group. Cautious interpretation is required when comparing treatment groups to one another (VAD-DT, VAD-OHT, and OHT-alone) in terms of persistence of PH and related hemodynamic data given each group inherently possess its own selection bias, particularly survival bias in VAD-DT. Second, lack of comprehensive medication data, post-intervention laboratory data, information on complications specific to treatment received, adjunctive mechanical therapies (intra-aortic balloon pump and RV assist device), duration of HF, and heterogeneity in device implantations (Supporting Information: Table 4) are potential confounders which could under- or over-estimate the PH prevalence and its impact on RVD. Third, missing RHC data was present in the study, largely at post-VAD RHC in both VAD-OHT and VAD-DT groups (Supporting Information: Table 5). While RHC after VAD is recommended, it is not always routinely performed on all patients and can be patient- and clinician-dependent. Also, the proportion of missing

data improved at post-OHT relative to post-VAD in the VAD-OHT group. In VAD-DT patients missing data was mostly attributable to patient death as can be seen from the near equal numbers of missing datapoints (Supporting Information: Table 5) and patients who died after VAD implantation (Supporting Information: Table 5). These conclusions support randomly missing data in these groups. However, it is also possible that hemodynamic assessments were performed for clinical concern or complication that cannot be conclusively excluded, which may unfavorably bias post-VAD RHC values. Therefore, careful interpretation of the conclusions is prudent and post-VAD RHC surveillance requires further study. Fourth, limited serial hemodynamic data >1 year after final intervention limited extended evaluation of the time-varying effect of pulmonary pressures. Fifth, specific indications for selection of treatment received (VAD implantation and/or OHT transplantation) along with rationale for ineligibility for OHT in VAD-DT may elucidate the impact on PH persistence and/or RVD at each RHC. The limitations discussed above would have an impact on both RVD and PH presence in the post-intervention setting (VAD and/or OHT) and would be important in predicting patients at risk and those who would benefit from close hemodynamic evaluation.

The strengths of our study include the longitudinal evaluation of RHC-based hemodynamics, impact of PH persistence based on PH-subtype and intervention received (VAD, OHT, or both), and the impact of PH persistence on survival. Our study is able to demonstrate despite effective LV unloading and significant reduction in PH, a notable proportion of patients exhibit PH post-VAD and post-OHT with the latter associated with reduced survival 1-year after final intervention; however, and as importantly, a larger proportion of patients exhibit a remarkable level of elevated RAP and mPAP with suppressed PaPi suggestive of underlying derangements of RV function. Though further investigation is needed to confirm our findings in other similar cohorts, it is especially prudent to evaluate whether hemodynamic optimization in post-VAD-assisted patients or close follow-up RHC surveillance in select post-VAD and/or post-OHT patients exhibiting RVD may subsequently improve patient outcomes.

AUTHOR CONTRIBUTIONS

Arun Rajaratnam: Conceptualization; data curation; formal analysis and interpretation; methodology; validation; writing and editing; guarantor. **Ameen El-Swais**: Data acquisition; data curation; investigation. **Floyd W. Thoma**: Data acquisition. **Moaaz O. Baghal**: Data acquisition. **Kristen Raffensperger**: Data acquisition. **Chung-Chou H. Chang**: Formal analysis and interpretation. **Gavin W. Hickey**: Formal analysis and interpretation; review and editing. **Faraaz A. Shah**: Formal analysis and interpretation; writing, review and editing. **Imad Al Ghouleh**: Conceptualization; data curation; formal analysis and interpretation; methodology; validation; writing and editing; guarantor. All authors contributed to the drafting, review, and revised manuscript and gave final approval for submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was approved by the University of Pittsburgh Institutional Review Board (STUDY20090170).

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