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The role of sensitization in post-transplant outcomes in adults with congenital heart disease sensitization in adults with congenital heart disease

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ABSTRACT

Introduction: The number of heart transplants in adults with congenital heart disease (CHD) is increasing, though outcomes remain unfavorable compared to those without CHD. The etiology of this mortality difference remains uncertain. Panel reactive antibody (PRA) is a predictor of survival post-transplantation, and adult CHD patients have been observed to have higher PRA levels. Here we assessed the relationship between PRA and outcomes in adult patients with CHD who underwent heart transplantation.

Methods: This is a retrospective cohort study using the 2004–2015 ISHLT Thoracic Organ Transplant Registry to investigate the role of sensitization in the observed excess mortality. The composite outcome of mortality or graft failure within 1-year of transplantation was compared among CHD vs. non-CHD recipients, according to sensitization as measured by pre-transplant panel reactive antibodies (PRA).

Results: Adults with CHD (n = 1188) had higher PRA level compared to non-CHD (n = 38,201) recipients (27% vs. 18% PRA>10%, respectively, $p < 0.001$). CHD diagnosis remained independently associated with a higher incidence of the composite outcome in multivariable analysis after adjusting for PRA and other variables. Further, even after age-matching, patients with CHD and PRA ≤10% were at higher risk of the primary outcome compared to non-CHD (OR 2.1 [1.4–3.4], p = 0.001), though both groups had comparable outcomes when PRA was >10% (OR 1.1 [0.6–2.0], p = 0.852).

Conclusions: Adults with CHD are more likely to have higher sensitization and worse outcomes than non-CHD recipients. Higher sensitization rates alone do not fully explain their excess risk of adverse outcomes after heart transplantation.

1. Introduction

The number of adult patients living with congenital heart disease (CHD) is increasing, many of whom eventually develop heart failure, accounting for over 17,000 inpatient admissions annually in the United States and significant morbidity and mortality [1–4]. Some patients with CHD have abnormal structural anatomy and a history of prior surgery, making them poor candidates for mechanical circulatory support [5]; thus, heart transplantation is often the only intervention available.

Patients with CHD have significantly higher 1-year post-transplant mortality than non-CHD patients [6,7], though the etiology of this difference is poorly understood. Despite the lack of therapeutic alternatives, this excess risk [6–10] often limits transplant availability to CHD patients. That is particularly notable because CHD patients have better

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long-term survival compared to age-matched non-CHD counterparts [6].

The increased risk of 1-year mortality has been attributed to the complex anatomy and sensitization/rejection, though there has been limited systematic investigation. Patients with CHD are thought to have higher panel reactive antibody (PRA) levels, an indicator of sensitization status [11], due to a history of multiple surgical interventions, blood transfusions, and prosthetic material during surgical repairs. However, whether or not high PRA levels are associated with the poor outcomes seen in adult CHD patients is uncertain.

Establishing risk factors for increased early mortality may help centers identify those CHD patients more likely to do well post-transplant. Thus, we examined the pre-transplant PRA level as a potential predictor of short-term post-transplant mortality in adults with CHD compared to those without CHD.

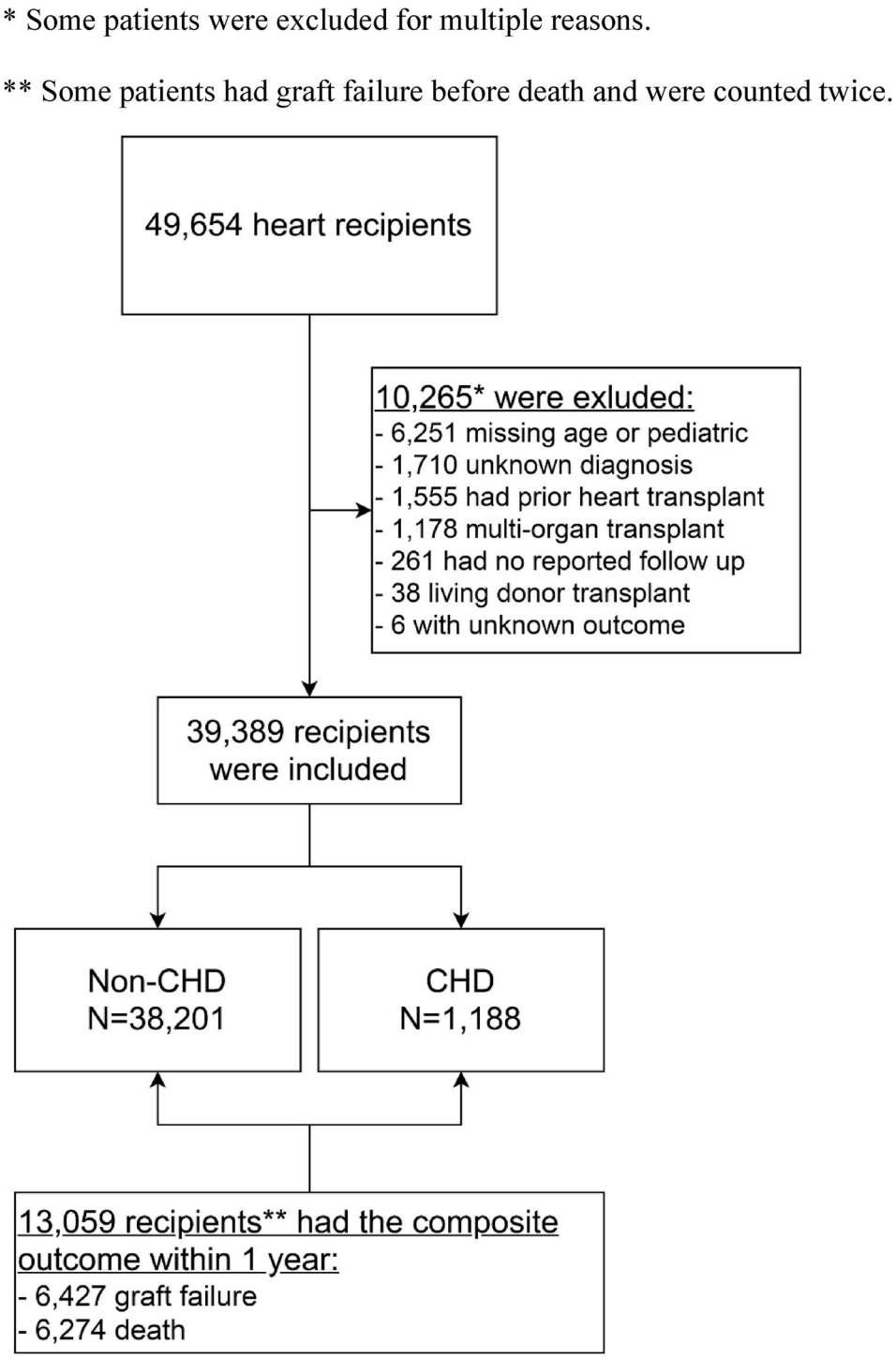

Fig. 1. Cohort selection.
* Some patients were excluded for multiple reasons.
** Some patients had graft failure before death and were counted twice.

2. Methods

2.1. Study population

This is a retrospective cohort study of adult patients (≥18 years) who underwent heart transplantation between July 1, 2004, and June 30, 2015, using data collected by the International Society for Heart and Lung Transplantation (ISHLT) Thoracic Organ Transplant Registry. Patients with CHD (n = 1188) and without CHD (n = 38,201) were included; recipients of multiple organs or repeat transplantation were excluded. Fig. 1 summarizes cohort selection for the present study. Partners HealthCare/Brigham and Women's Hospital (Partners Human Research Committee) approved the study.

2.2. Clinical endpoints and PRA

The primary aim of this study was to assess the relationship between PRA levels and all-cause mortality and graft failure in the first year post-transplant for patients with compared to those without congenital heart disease. The composite primary outcome used was composed of two components, all-cause mortality or graft failure within 1-year of transplantation. The secondary aims of the study were to assess the impact of other pre-transplant variables on the 1-year composite outcome, specifically the donor/recipient age, end-organ function (renal, hepatic), ischemic time, and transplant center volume.

Patients were observed from the time of transplantation until the occurrence of the primary outcome within 1 year of transplantation. United Network of Organ Sharing (UNOS) first approved using the calculated PRA (cPRA) in 2007; the single cPRA level replaced reporting separate class I and class II levels in March 2015 within the ISHLT Thoracic Organ Transplant Registry. The separate reporting of class I and class II PRA can be highly variable depending on the panel's composition used and laboratory technique for antibody detection [12]. The cPRA is calculated using an ethnically weighted reference database to reflect the percentage of actual organ donors who express ≥1 unacceptable HLAs [13]. Concordance between the separately reported class I and II PRA and the cPRA is high; for the most sensitized patients (PRA >80%), concordance is estimated to be 90%. For those with lower PRAs (1–80%), concordance varies from 50 to 68%, with the traditional class I and class II reporting underestimating sensitization compared to the cPRA [14]. Calculated PRA and class I and II PRA values were combined for the current analyses. Due to limitations of the ISHLT database, if class I and class II PRA values were reported separately (by most countries outside the United States), the higher of the two values was used (rather than the cPRA).

2.3. Statistical analysis

Summary statistics were reported for quantitative variables as median and 5th to 90th percentiles and as percentages for categorical variables. PRA was summarized in both continuous and categorical fashion (0%, 1–10%, and >10%). Categorical variables were compared across the diagnoses groups (CHD vs. non-CHD) using the chi-square test, whereas continuous variables were compared using the Kruskal Wallis test. One-year rates of the composite outcome were compared across diagnoses groups and PRA categories using the contingency table method with Cochran-Mantel-Haenszel test. Because age is a strong predictor of outcomes, and most adults with CHD were relatively younger than their counterparts, a propensity score of 1:1 matching on age between CHD vs. non-CHD recipients was performed. Recipients with missing PRA values were excluded from the matched analysis.

Multivariable logistic regression model was used to examine the association between the primary outcome and diagnosis group, PRA, and other independent variables. Interaction between diagnosis and PRA was examined but not included in the final model. Unless specified otherwise, continuous risk factors (including PRA) were included in the multivariable model using a restricted cubic spline to allow for the most flexible fit of the functional form. Missing values were computed using the multiple imputation method (n = 30 imputations). The logistic model results were presented in tabular format for each of the categorical independent variables. For significant continuous variables, the results were displayed in graphical format. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS v9.3 (SAS Institute, Inc., Cary, NC.) and R Core Team (2016) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/).

3. Results

In total, 39,389 heart transplant recipients were included in the analysis (Fig. 1). Table 1 lists the baseline characteristics of the unmatched study cohort. Patients with CHD (3%) were significantly younger than those without CHD. Most patients were male, though this sex difference was less pronounced in the CHD cohort.

Overall, there was higher sensitization among CHD patients; 27% had a PRA >10%, compared to 18% of non-CHD patients (p < 0.001). There was a wide distribution of PRA levels among CHD patients, and patients with CHD were over-represented within all PRA categories above 10% (Fig. 2).

The rate of the composite outcome in the age-matched cohort is shown in Fig. 3. There was a statistically significant increased risk of the composite outcome for CHD patients within the low (0% PRA) and intermediate (0–10% PRA) PRA categories (combined OR for CHD vs. non-CHD 2.2 [1.5 to 3.4], p = 0.0001). Patients with the highest sensitization (PRA >10%) had the highest rate of the composite outcome; however, there was no significant difference between those with and without CHD (OR 1.1 [0.6 to 2.0], p = 0.852). Even after adjusting for PRA, CHD diagnosis remained a strong and independent predictor of the composite

Table 1
Baseline characteristics by congenital heart disease category.

Characteristics	Non-CHD (N = 38,201)	CHD (N = 1188)	p-value
Recipient Age (years)	55.0 (26.0–67.0)	35.0 (18.4–60.0)	<0.001
Donor Age (years)	35.0 (17.0–57.0)	31.0 (15.0–55.0)	<0.001
Recipient Sex (female)	8875 (23.2%)	443 (37.3%)	<0.001
Recipient BMI (kg/m^2)	26.3 (19.5–35.1)	23.4 (17.4–33.4)	<0.001
Donor/Recipient Weight Ratio	1.00 (0.74–1.45)	1.06 (0.77–1.610)	<0.001
History of Diabetes	5661 (25.7%)	33 (4.69%)	<0.001
Recipient Hospitalized	9264 (44.0%)	332 (52.1%)	<0.001
Recipient PRA			<0.001
0%	12,580 (67.4%)	327 (58.7%)	
1%–10%	2824 (15.1%)	81 (14.5%)	
>10%	3267 (17.5%)	149 (26.8%)	
Recipient eGFR (mL/min/1.73 m^2)	78.2 (39.1–115)	89.9 (37.9–180)	<0.001
Recipient Bilirubin (mg/dl)	0.80 (0.30–2.90)	0.90 (0.30–3.59)	0.003
Ischemic Time (hours)	3.25 (1.57–5.07)	3.53 (1.68–5.74)	<0.001
Adult Heart Center Volume	19.0 (5.0–70.0)	19.0 (1.0–64.0)	0.019
Adult CHD Center Volume	0.0 (0.0–3.0)	1.0 (0.0–5.0)	<0.001

Key recipient, donor, surgical and center characteristics for adult heart transplant recipients stratified by CHD status (unmatched cohort). The distribution of continuous variables is reported as median and 5th to 95th percentiles, and percentages for categorical variables. Comparisons for the individual and group characteristics between CHD vs. non-CHD strata were performed using Chi-square test for categorical variables or the Kruskal Wallis test for continuous variables. CHD, congenital heart disease; BMI, body mass index. PRA, panel reactive antibodies; eGFR, estimated glomerular filtration rate.

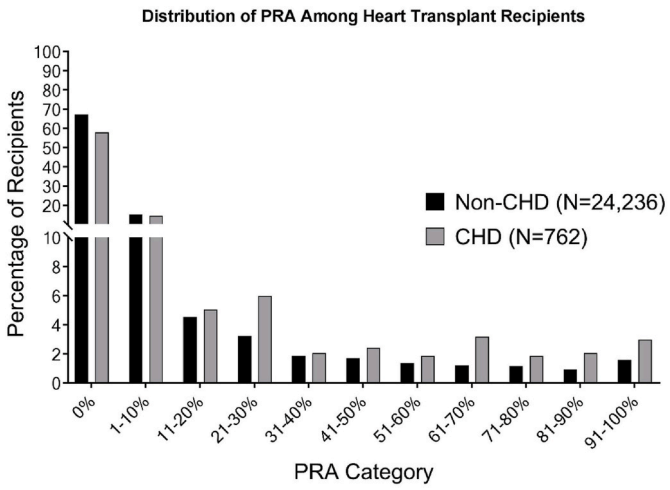

Fig. 2. Distribution of PRA among heart transplant recipients, stratified by congenital heart disease status.

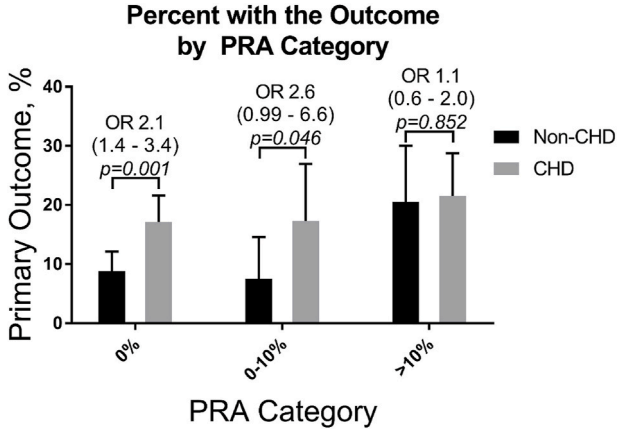

Fig. 3. Percent with the composite outcome by PRA subset.
Heart transplant recipients with a history of CHD who had a PRA either 0% or 0–10% had worse outcomes than patients with no CHD. Both groups were comparable among those with elevated PRA >10%. PRA, panel reactive antibodies; CHD, congenital heart disease; OR, odds ratio.

outcome (mortality or graft failure at 1 year). Additionally, PRA was a significant independent predictor; the higher the PRA, the higher the odds of the composite outcome, peaking at a PRA of 100% associated with approximately 40% risk of death or graft failure, Table 2 Fig. 4. The data confirm that patients with CHD have overall higher PRA levels than age-matched non-CHD patients. Higher PRA levels were associated with higher composite outcome rates in both cohorts. However, after accounting for the PRA level, there was still a higher rate of the composite outcome in patients with CHD, suggesting PRA contributed to but did not explain the differences between the groups.

Multivariate analysis was used to assess the impact of other pre-transplant factors on the composite outcome. Female recipients and hospitalization at the time of transplant were identified as independent categorical predictors of the composite outcome. Young donor and recipient age (<35 and < 55 years, respectively), shorter ischemic time, and normal hepatic function were associated with a lower rate of the composite outcome. Higher volume transplant centers performing above 20 transplants per year was also associated with lower composite outcome. The donor/recipient weight ratio showed a strong but statistically non-significant association with the primary outcome.

Table 2
Categorical multivariable risk factors for one-year composite outcomes[a].

Variable	Odds Ratio	P-value
Diagnosis CHD vs. non-CHD	1.63 (1.40–1.90)	<0.0001
Recipient sex female	1.19 (1.10–1.28)	<0.0001
Recipient diabetes	1.05 (0.96–1.15)	0.26
Recipient hospitalized vs. not	1.20 (1.09–1.32)	0.0001

CHD, congenital heart disease; ICU, intensive care unit.

[a] The listed risk factors were entered in a multivariable logistic regression model, including continuous risk factors depicted in Fig. 2.

4. Discussion

In this large cohort study of adults who received a heart transplant, patients with CHD had significantly higher PRA levels than patients without CHD. Higher PRA was independently associated with increased risk of the composite outcome (mortality or graft failure at 1 year), particularly for those with a PRA >10%. However, after accounting for PRA level in an age-matched cohort, there was a significant increase in the composite outcome for patients with CHD compared to those without (Fig. 3). Thus, the increased PRA levels observed in patients with CHD contributed to but did not fully explain the poor 1-year outcomes consistently observed in this population.

Higher PRA levels among adults with CHD are consistent with previously published literature [15]. Patients with CHD typically require multiple surgical interventions throughout childhood and adolescence, often exposing them to blood products, biologic material (such as homografts), and synthetic material [15]. Additionally, many require anticoagulation which may predispose to bleeding and blood transfusions. Multiple pediatric studies have demonstrated that higher PRA levels independently predict post-transplant mortality [10,16,17]. We found that even after controlling for PRA level in an aged-matched cohort, patients with CHD had significantly higher 1-year mortality or graft failure.

Once PRA levels were above 10%, the rate of composite outcome was similar for those with and without CHD. This suggests that while higher PRA levels remain an important issue in the selection of transplant recipients, a level >10% is not any more important in a patient with CHD than one without CHD.

CHD patients share many established risk factors for poor post-transplant outcomes with non-CHD patients [18]. Younger donor and recipient age and shorter ischemic time were unsurprisingly associated with lower composite outcome. While it was observed that the CHD population was younger and received younger donor organs, they had significantly longer ischemic time, which was also an independent predictor of the composite outcome. Given the significant difference in ischemic time between the two groups, the difference may be related more to complex anatomy and technical/surgical factors than transportation time and workflows. This highlights the importance of performing transplants in patients with CHD at experienced transplant centers. Nguyen et al. reported significantly improved post-transplant outcomes among CHD patients undergoing transplantation at high-volume centers for CHD care [19]. Similarly, we demonstrated a decreased risk of the composite outcome at centers performing more than 20 transplants annually.

Similar to previously published UNOS data [20], this study also observed that women were the minority gender for both CHD and non-CHD patients who received a heart transplant. Historically, women have had worse outcomes on the waitlist and in the post-transplant period [21,22]. One small study showed improving outcomes for women with the updated listing criteria [23], though calls remain for further modifications to listing criteria to create more gender equality [22]. Similar to prior studies, we demonstrated that the female sex was an independent risk factor for death or graft failure at 1-year post-transplantation. The exact etiology of the gender differences remains under investigation, though it has been postulated that increased estrogen levels, multiparity, and donor-recipient sex mismatch may be

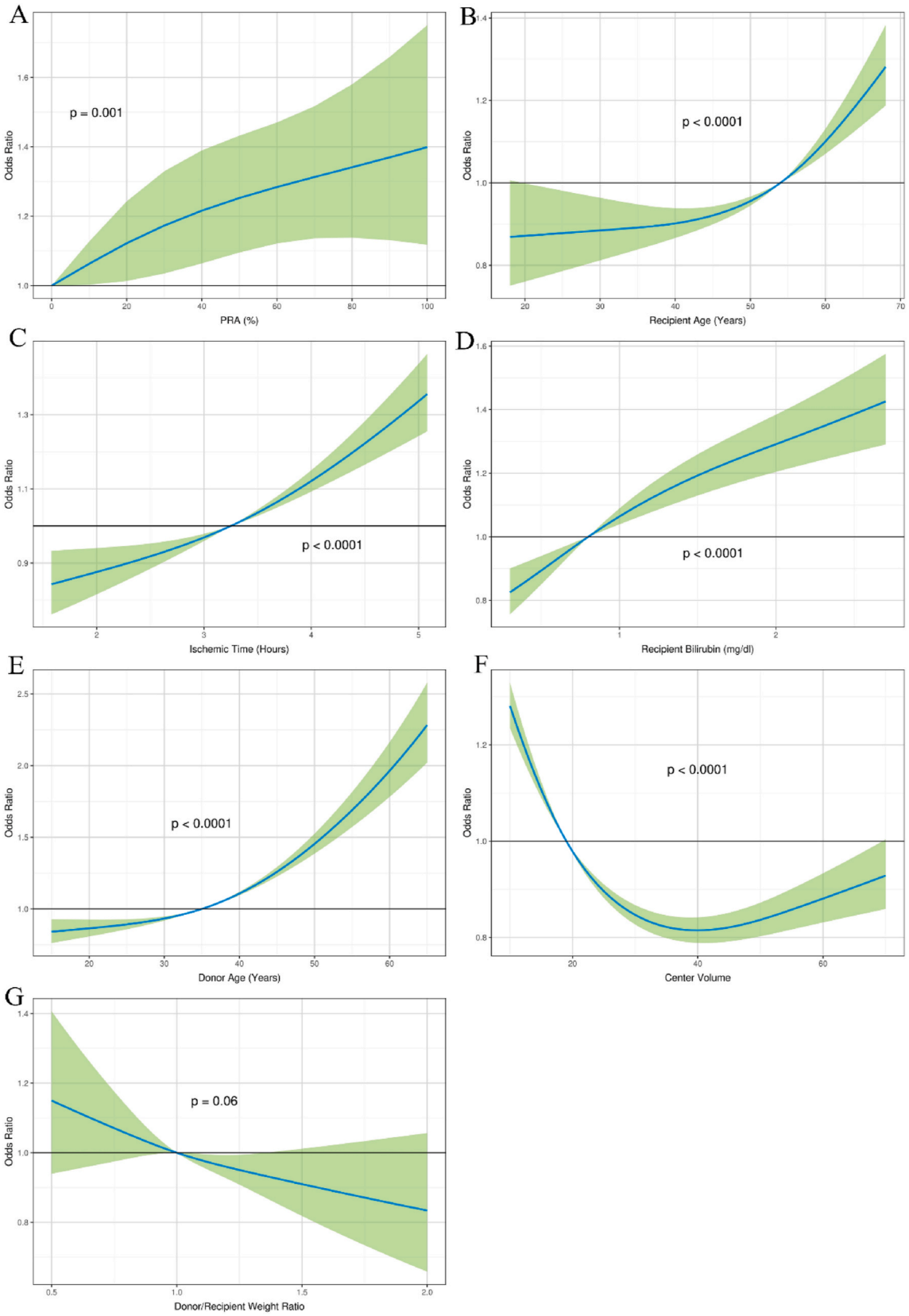

Fig. 4. Continuous multivariable risk factors for the composite outcome within 1 year of transplantation.
There was a negative relationship between PRA (A), recipient age (B), ischemic time (C), recipient bilirubin (D), and donor age and the primary outcome. There was an inverse relationship between center volume (F) and the primary outcome, whereas donor/recipient weight ratio was less strongly associated with the primary outcome. The blue line marks the odds ratio, and the green shaded area represents 95% confidence intervals.

risk factors [24–26]. Multiparous women with CHD may be at particularly high risk for elevated PRA levels and poor post-transplant outcomes, though a dedicated investigation is needed to assess this group.

In conclusion, while the overall higher PRA levels observed in CHD patients did not fully explain the elevated composite outcome, it remains an important factor in patient selection. Patients in this study with a PRA >10% had the highest risk of composite outcome; however, there was no difference within this high PRA subgroup between those with and without CHD. Thus a PRA level >10% is an important consideration for transplant selection, though it should not be weighted differently in a CHD vs. non-CHD patient.

This study has several limitations. This database does not comprehensively capture CHD diagnosis, so it is not possible to refine this heterogeneous group of patients. PRA was used as a surrogate for sensitization status, but it may not capture the full spectrum of allosensitization, as it has been hypothesized that those with protein-losing enteropathy where immunoglobulin levels are low may limit the use of PRA as a determinant of sensitization status. Additionally, gravity and parity were not captured for female patients, which may have impacted PRA levels and contributed to the gender discrepancies in the composite outcome. Furthermore, the PRA does not predict anamnestic response following organ transplantation, an essential consideration in those whose sensitizing event may have been decades before transplantation. Nevertheless, PRA is a widely utilized and easily attainable measure of sensitization. A 12-month time point was selected based on previously published literature, though there may be additional discrepancies in outcomes between CHD and non-CHD patients that emerge after 12 months when immunosuppression medications begin to taper. Further, by including a composite outcome within the 12 months, there may be an overrepresentation of early 30-day mortality in the CHD population attributable to increased surgical complexity. Lastly, there could be residual confounders that were not accounted for in the multivariable model or age-matched analyses.

In conclusion, this large registry analysis found that adults with CHD are more likely to be sensitized than adults without CHD. Sensitization was an independent risk factor for graft failure or death within 1 year of transplantation but did not fully explain the disparity in outcomes among CHD patients.

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Disclosures

Dr. Rossano has conflicts of interest to disclose as described by the *American Journal of Transplantation*: he reports personal fees from Amgen, personal fees from Novartis, personal fees from Bayer, personal fees from Abiomed, outside the submitted work. Other authors have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

Data availability statement

The data supporting the findings of this study are available from the ISHLT Thoracic Organ Transplant Registry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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