Indexed donor cardiac output for improved size matching in heart transplantation: A United Network for Organ Sharing database analysis

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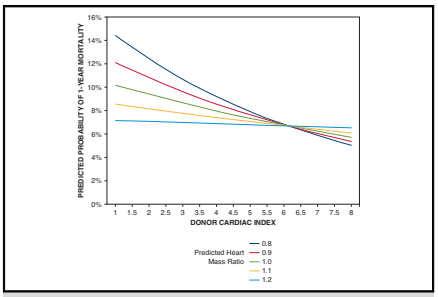
ABSTRACT

Objective: Implantation of an appropriately sized donor heart is critical for optimal outcomes after heart transplantation. Although predicted heart mass has recently gained consideration, there remains a need for improved granularity in size matching, particularly among small donor hearts. We sought to determine if indexed donor cardiac output is a sensitive metric to assess the adequacy of a donor heart for a given recipient.

Methods: A retrospective analysis was performed (2003-2021) in isolated orthotopic heart transplant recipients from the United Network for Organ Sharing database. Donor cardiac output was divided by recipient body surface area to compute cardiac index (donor cardiac index). Predicted heart mass ratio was computed as donor/recipient predicted heart mass. The primary outcome was mortality 1 year after transplant.

Results: Among transplant recipients, median donor cardiac output was 7.3 (5.8-9.0) liters per minute and donor cardiac index was 3.7 (3.0-4.6) liters per minute/m^2. Predicted heart mass ratio was 1.01 (0.91-1.13). After multivariable adjustment, higher donor cardiac index was associated with lower 1-year mortality risk (odds ratio, 0.92, $P = .042$). Recipients with predicted heart mass ratio less than 0.80 (n = 255) had a lower median donor cardiac index than those with a predicted heart mass ratio of 0.80 or greater (3.2 vs 3.7, $P < .001$). As predicted, heart mass ratio became smaller and the association between donor cardiac index and 1-year mortality became progressively stronger.

Conclusions: Higher donor cardiac index was associated with a lower probability of 1-year mortality among patients undergoing heart transplantation and served to further quantify mortality risk among those with a small predicted heart mass ratio. Donor cardiac index appears to be an effective tool for size matching and may serve as an adjunctive strategy among small donor hearts with a low predicted heart mass ratio. (JTCVS Open 2023;15:291-9)



Association of mortality and dCI stratified by PHMr.

CENTRAL MESSAGE

The dCI may represent a valuable additional metric to assess the size and quality of a donor heart for a particular recipient.

PERSPECTIVE

In this cohort study of 3615 patients undergoing heart transplantation with a donor right heart catheterization, greater dCI was strongly associated with lower 1-year mortality risk. However, more important, the impact of dCI on mortality became more substantial with smaller PHMrs.

Donor-recipient heart size matching has been shown to be critically important in outcomes after heart transplantation.[1] The ideal metric to match donor hearts to recipient body size has evolved over time. Although body weight and height have been commonly used, predicted heart mass ratio (PHMr) has been established recently as a potentially improved metric for sizing.[2-4]

Recipients who receive a donor heart with a low PHMr are at a potentially increased risk for morbidity after transplantation; therefore, these hearts often are not used.[3] However, a subset of these hearts are likely appropriate for transplantation, and additional methods are needed to determine which donor hearts for a given recipient are appropriate for transplantation.

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Abbreviations and Acronyms

BSA = body surface area
dCI = donor cardiac index
IQR = interquartile range
LPM = liters per minute
OR = odds ratio
PHMr = predicted heart mass ratio
UNOS = United Network for Organ Sharing

At our institutions, we began using donor cardiac output as another method to determine the adequacy of donor heart size for a particular recipient. We hypothesized that donor cardiac output, indexed to recipient body surface area (BSA), would be highly associated with survival, particularly among donor hearts with a small PHMr.

MATERIALS AND METHODS

Study Design

A retrospective database analysis was performed using the Organ Procurement and Transplant Network Standard Transplant Analysis and Research thoracic database, administered by United Network for Organ Sharing (UNOS). This study was approved by the local Institutional Review Board with a waiver of the need of individual consent (HP-00105689, 5/1/2023). The UNOS database was queried for all isolated heart transplant recipients aged 18 years or more between 2003 and 2021. Among this cohort, patients were only included if donor right heart catheterization data and recipient BSA were available (N = 3619). Cardiac output was only calculated on the basis of right heart catheterization, and not bioimpedance. Strong outliers were removed, leaving a final cohort of 3615 patients available for analyses.

Donor cardiac index (dCI) was calculated as donor cardiac output divided by recipient BSA at listing. Donor cardiac output was calculated using the initial cardiac output variable, and if not available, using the final cardiac output variable as defined in the UNOS database.

PHMr was calculated as previously reported using the following equation:

$$\textit{Predicted left heart mass} : \alpha * Height^{0.54}\ (meters) * Weight^{0.61}\ (Kg),\ \textit{where } \alpha = 6.82 \textit{ for women and } 8.25 \textit{ for men}$$

$$\textit{Predicted right heart mass} : \alpha * Age^{-0.32}\ (yrs) * Height^{1.135}\ (meters) * Weight^{0.315}\ (Kg), \textit{where } \alpha = 10.59 \textit{ for women and } 11.25 \textit{ for men}$$

Predicted heart mass (PHM) was calculated by adding predicted left and right heart mass. PHMr was calculated by dividing donor PHM by recipient PHM.

Statistical Analysis

All analyses were conducted with SPSS Statistics for Windows, Version 28.0 (IBM Corp), and the alpha level was set at P less than .05, 2-tailed. The Kolmogorov–Smirnov normality test was performed for all continuous variables, and the appropriate statistical test is reported. Continuous variables are presented as median (interquartile range [IQR]), and categorical variables are presented as frequency (percent). Patient and surgical characteristics were compared using Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables. Associations between continuous variables were conducted using Spearman correlation analyses. Univariate associations of dCI as a continuous variable to dichotomous outcomes were examined with logistic regression analyses. Multivariable logistic regression analysis examined the association of dCI to outcomes after adjustment for recipient age, recipient sex, recipient hospitalization status at transplant, preoperative left ventricular assist device, and donor inotropes. Subsequent analyses included PHMr and the interaction of dCI and PHMr to further understand the role of both of these factors on outcomes.

RESULTS

There were 3615 patients identified with donor right heart catheterization and recipient BSA data available. Median recipient age was 56 years, 23% were female, and the most common diagnosis was dilated cardiomyopathy. Median donor age was 35 years, and 29% were female (Table 1). Median donor cardiac output was 7.3 LPM (IQR, 5.8-9.0), and median dCI was 3.7 LPM/m^2 (IQR, 3.0-4.6). Greater recipient weight ($r_s = -0.18$, $P < .001$)

TABLE 1. Recipient and donor characteristics

Characteristics	N = 3615
Recipient characteristics	
Age (y)	56 (46-62)
Female sex	847 (23)
PHM (g)	184 (160-205)
Weight (kg)	82 (70-94)
Height (m)	1.8 (1.7-1.8)
BMI (kg/m^2)	27 (24-30)
BSA (m^2)	2.0 (1.8-2.2)
Creatinine (mg/dL)	1.2 (1.0-1.5)
PA systolic pressure (mm Hg)	40 (31-50)
Diagnosis	
Dilated cardiomyopathy	2969 (82)
Ischemic cardiomyopathy	250 (7)
Restrictive cardiomyopathy	102 (3)
Congenital	78 (2)
Other	216 (6)
MCS at transplant	
None	2228 (62)
LVAD	1190 (33)
RVAD/BiVAD/TAH (“all others”)	197 (5)
Donor characteristics	
Age (y)	35 (24-45)
Female sex	1054 (29)
PHM (g)	186 (162-207)
Weight (kg)	81 (70-94)
Height (m)	1.8 (1.7-1.8)
BMI (kg/m^2)	27 (23-30)
Transplant characteristics	
Ischemic time (h)	3.3 (2.6-3.9)
Female donor to male recipient	571 (16)

Data presented as n (%) or median (IQR). *PHM*, Predicted heart mass; *BMI*, body mass index; *BSA*, body surface area; *PA*, pulmonary artery; *MCS*, mechanical circulatory support; *LVAD*, left ventricular assist device; *RVAD*, right ventricular assist device; *BiVAD*, biventricular assist device; *TAH*, total artificial heart.

and BSA ($r_s = -0.17$, $P < .001$) were also significantly, but weakly, correlated with lower dCI.

Donor cardiac output, not indexed to the recipient, was positively correlated with donor PHM ($r_s = 0.36$, $P < .001$). Donor height ($r_s = 0.23$, $P < .001$), weight ($r_s = 0.29$, $P < .001$), body mass index ($r_s = 0.19$, $P < .001$), and BSA ($r_s = 0.31$, $P < .001$) were also positively correlated with donor cardiac output.

Donor Cardiac Index and Outcomes

The incidence of outcomes in this sample was 16% acute rejection (572 of 3605), 3% postoperative stroke (117 of 3574), 11% postoperative dialysis (403 of 3583), 3% postoperative pacemaker (97 of 3572), 20% rejection within 1 year (588 of 3023), 11% mortality within 1 year (406 of 3615), and 22% mortality within 5 years (785 of 3614). On univariate analysis, there was a significant association of greater dCI with reduced risk for 1-year mortality (odds ratio [OR], 0.91 per LPM/m^2 increase in dCI, $P = .031$; Table E1). Greater dCI was associated with reduced risk of postoperative dialysis requirement, but this analysis did not reach statistical significance (OR, 0.95, $P = .186$). After covariate adjustment, the risk for 1-year mortality associated with dCI remained similar (OR, 0.92, $P = .042$; Figure E1, Table 2).

Predicted Heart Mass Ratio and Outcomes

Among this cohort of patients, median PHMr was 1.01 (IQR, 0.91-1.13). On univariate analysis, greater PHMr was associated with reduced risk for postoperative dialysis requirement (OR, 0.50, $P = .024$) and reduced risk for 1-year mortality, although the latter analysis did not reach statistical significance (OR, 0.58, $P = .066$; Table E2). After multivariable adjustment, greater PHMr was significantly associated with reduced risk for 1-year mortality (OR, 0.43, $P = .011$; Table E3).

Donor Cardiac Index and Predicted Heart Mass Ratio Relationship

Greater dCI was significantly correlated with greater PHMr, but was not a strong association ($r_s = 0.29$, $P < .001$). When separated by PHMr less than 0.80 and 0.8 or greater, the median dCI for the PHMr less than 0.80 was 3.2 (IQR, 2.7-3.9) LPM/m^2 compared with 3.7 (IQR, 3.0-4.6) LPM/m^2 for the PHMr 0.8 or greater group ($P < .001$, Figure E2). There were 0.7% of patients receiving a heart transplant who had a PHMr less than 0.8, but a dCI greater than the 75th percentile.

TABLE 2. Multivariable logistical regression model to assess the relationship between donor cardiac index and 1-year mortality

Variable	OR	95% CI	*P* value
Recipient age, y	1.02	1.01-1.02	.001
Female recipient	1.16	0.91-1.48	.247
Recipient hospitalized	1.44	1.16-1.78	<.001
Preoperative LVAD	1.23	0.99-1.53	.067
Donor inotropes	1.13	0.91-1.39	.274
dCI per 1 LPM/m^2	0.92	0.84-0.997	.042

OR, Odds ratio; *CI*, confidence interval; *LVAD*, left ventricular assist device; *dCI*, donor cardiac index; *LPM*, liters per minute.

Donor Cardiac Index, Predicted Heart Mass Ratio, and Outcomes

When considering both dCI and PHM in multivariable analysis, there appeared to be an important interaction between dCI and PHMr on 1-year mortality (Table 3). Although the interaction itself did not quite reach statistical significance in the multivariable model (PHMr by dCI interaction, $P = .075$), this result suggests the possibility of PHMr modifying the relationship between dCI and survival. Therefore, the regression equation from this model was used to illustrate the potential interaction effect, holding covariates at the mean or reference values and varying the input values for dCI and PHMr (Figure 1). As PHMr becomes smaller, the association between dCI and 1-year mortality becomes progressively stronger. For example, when PHMr is high, there is almost no relationship between dCI and mortality. But when PHMr is low, the risk for mortality decreases as dCI increases. Based on the regression equation from this multivariable model, a donor heart with a PHMr of 0.8, but a dCI of 3.45 LPM/m^2 would have a predicted probability of 1-year mortality of 10%. Within those with PHMr less than 0.8, 38% of recipients had a dCI of 3.45 or greater.

Assessment of Selection Bias

The cohort that had donor right heart catheterization data available to calculate dCI for this study represented 5% of the total adult cohort with isolated orthotopic heart

TABLE 3. Multivariable logistic regression model to assess the relationship among donor cardiac index, predicted heart mass ratio, and survival

Variable	Odds ratio	95% CI	*P* value
Recipient age, y	1.02	1.01-1.03	<.001
Female recipient	1.31	0.997-1.72	.052
Recipient hospitalized	1.45	1.17-1.80	<.001
Preoperative LVAD	1.23	0.99-1.54	.060
Donor inotropes	1.14	0.92-1.40	.233
dCI per 1 LPM/m^2	0.66	0.43-0.99	.044
PHMr	0.12	0.02-0.67	.015
PHMr * dCI	1.41	0.97-2.05	.075

PHMr * dCI represents the interaction of PHMr and dCI. *CI,* Confidence interval; *LVAD*, left ventricular assist device; *dCI*, donor cardiac index; *LPM*, liters per minute; *PHMr*, predicted heart mass ratio.

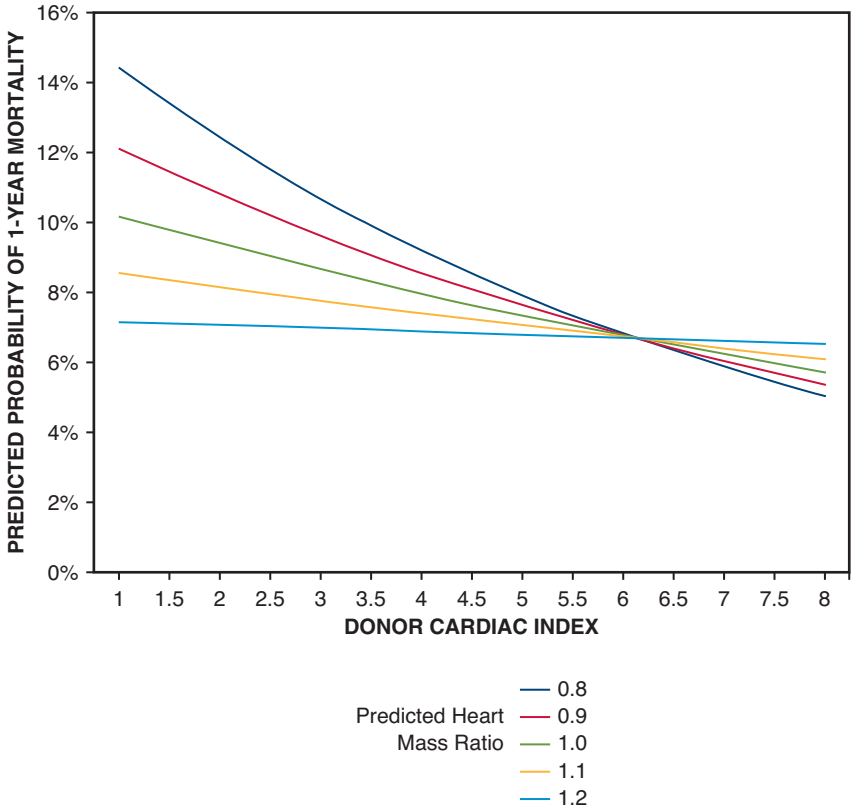

FIGURE 1. Graph illustrating the interaction effect of dCI and PHMr on 1-year mortality using the regression equation from the multivariable logistic regression analysis, holding covariates at mean and reference values and varying the input values for dCI and PHMr. The plot indicates that as PHMr becomes smaller, there is a more substantial effect of increasing dCI on reducing risk for 1-year mortality. *Top right* numbers indicate PHMrs.

transplant (N = 70,100). Although there were significant differences in patient and donor characteristics between those included in this study and those excluded for missing donor cardiac output (Table E4), many of these did not translate to meaningful clinical differences, such as a year difference in recipient age and 2-point difference in recipient PHM. Recipient pulmonary vascular resistance was not significantly different among donors who received a right heart catheterization compared with those who did not ($P = .119$). In addition, the incidence of outcomes was assessed between the included and excluded patients. There were fewer patients in the included cohort with acute rejection (16% vs 18%, $P = .002$), postoperative pacemaker (2.7% vs 3.4%, $P = .033$), and 1-year rejection (20% vs 29%, $P < .001$). However, the primary outcome of interest for this study was 1-year mortality, which did not differ between the included and excluded patients (11% vs 12%, $P = .133$).

DISCUSSION

These data demonstrate that dCI can serve as an additional metric to understand whether a donor heart is of adequate size and quality for a particular recipient. We found that as PHMr became smaller, the impact of greater dCI on reducing risk for mortality became more substantial.

On the basis of these data, we propose a novel algorithm for donor heart sizing that includes both PHMr and dCI (Figure 2). If PHMr is high, the heart size is likely adequate for transplant. However, if the PHMr is low, then clinicians should consider the dCI. If the dCI is high, then the heart size is likely adequate for transplant. If the dCI is also low, then the heart should be rejected for inadequate heart size. The definitions of "high" and "low" are intentionally vague, because each donor and recipient is unique, and factors such as elevated pulmonary vascular resistance and preoperative ventricular assist device are known risk factors where clinicians may want to use a higher PHMr or dCI.

PHMr has gained credibility as an improved metric for donor heart sizing compared with previously commonly used measures, including heart, weight, and BSA.[3,5-8] However, donor hearts with a PHMr less than 0.86 are often turned down, because they are considered too small relative to the recipient.[3] However, these data demonstrate that even those hearts with a small PHMr can be safely used in the setting of an adequate dCI. For instance, a donor heart with a PHMr of 0.8, but with a dCI of 5 LPM/m^2, had a

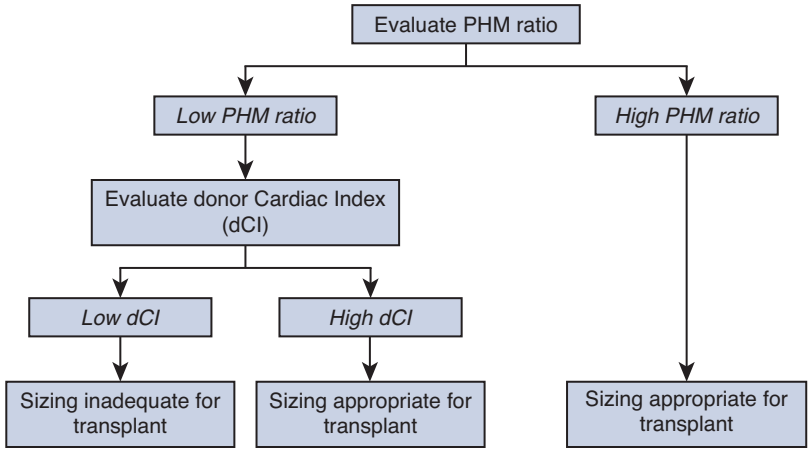

FIGURE 2. Proposed novel algorithm for donor heart sizing that includes both PHMr and dCI, based on the data in this study. *PHM*, Predicted heart mass.

predicted 1-year mortality less than 10% when applying the regression equation from these analyses. We hypothesize that among donor hearts with a larger PHMr, the effect of donor cardiac output on outcome is diminished because the heart is likely big enough or even oversized for the recipient, and hearts being used for transplant have normal or near-normal function.

Kransdorf and colleagues[3] compared PHM with other sizing metrics, including height, weight, body mass index, and BSA, and found that only severely undersized hearts with a PHMr less than 0.86 were associated with a significant hazard for 1-year mortality. During their study period, there were 64,407 offers turned down with a PHMr less than 0.86. Although the prevalence of adequate dCI is unclear, this metric provides the potential to increase the number of transplants within this large cohort of turned-down offers.

DCI provides a physiologic assessment of both donor size and quality, but can be impacted by a number of donor factors. Catecholamine release associated with neurologic death, volume status, and sepsis, among other factors, all influence donor cardiac output.[9-11] Therefore, as with all measures, these data must be taken in context of the donor. It was interesting to observe that the commonly used threshold of a cardiac index greater than 2.2 LPM/m^2 in postoperative cardiac surgery patients did not appear to be a useful threshold in these patients. We hypothesize that the catecholamine release associated with neurologic death creates a hyperdynamic, high cardiac output state and underlies much of the higher donor cardiac outputs seen and required in this cohort of patients.

Of note, there appears to be a considerable range of dCI even among patients with a low PHMr, consistent with the relatively weak correlation between dCI and PHMr. Among patients with a PHMr less than 0.8, the IQR for dCI was 2.7 to 3.9 LPM/m^2. Given that 25% of patients with PHMr less than 0.8 had a dCI greater than 3.9 LPM/m^2, which would represent a predicted 1-year mortality of 9.3% applying the regression equation from our interaction model, we believe this approach represents a realistic method with the potential to expand the usable donor heart pool. However, the dCI of small donor hearts that are turned down for transplant is not able to be quantified from this analysis, and future studies are needed to elucidate this information.

Study Limitations

This study has important limitations, including the observational and retrospective nature of this study. Given that only donors with a right heart catheterization were included in this study, there is the potential for selection bias. However, we attempted to better understand this bias by comparing patients included in this study with those excluded for a lack of right heart catheterization and found that although there were patient and donor characteristic differences, most represented small clinical differences. Although there may be differences in other unmeasured risk factors, the incidence of most outcomes (including 1-year mortality) was not different between included and excluded patients. For outcomes with differences, the incidences were lower in the included cohort, which could indicate that the associations with dCI and PHMr and those outcomes may be underestimated with this cohort.

A part of the variability in dCI may be due to variable heart rate and loading conditions. Unfortunately, given the lack of these data within the UNOS database at the time of right heart catheterization, we are not able to include load-independent analyses such as stroke work index or cardiac power. However, we believe that dCI provides clinicians with a relatively simple, usable metric when used in the appropriate clinical context. However, it is important to note that dCI should not be taken in isolation. dCI should be interpreted in the context of central venous pressure, pulmonary artery pressures, and wedge pressure.

Although included in our multivariable analysis, each transplant operation poses unique risks and the relationship among dCI, recipient perioperative morbidities, and mortality must be studied further. We were also unable to identify a specific threshold for dCI to recommend to physicians, because the relationship between dCI and mortality appears to be continuous, without a distinct threshold. However, it appears that those with a dCI above the median (3.7 LPM/m^2) have an acceptable 1-year survival regardless of PHMr.

CONCLUSIONS

dCI appears to be an important additional metric for clinicians to use in the context of PHMr and the particular recipient. dCI may allow for a greater donor pool and aid in curbing the donor heart shortage.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: donor heart sizing, heart allocation, heart transplantation

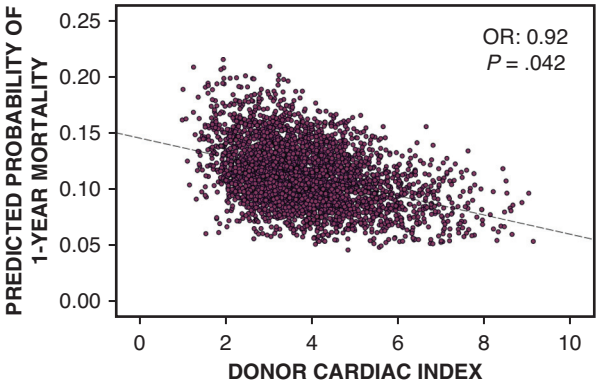

FIGURE E1. Scatterplot of dCI values with predicted probability of 1-year mortality values from the multivariable logistic regression model. *OR*, Odds ratio.

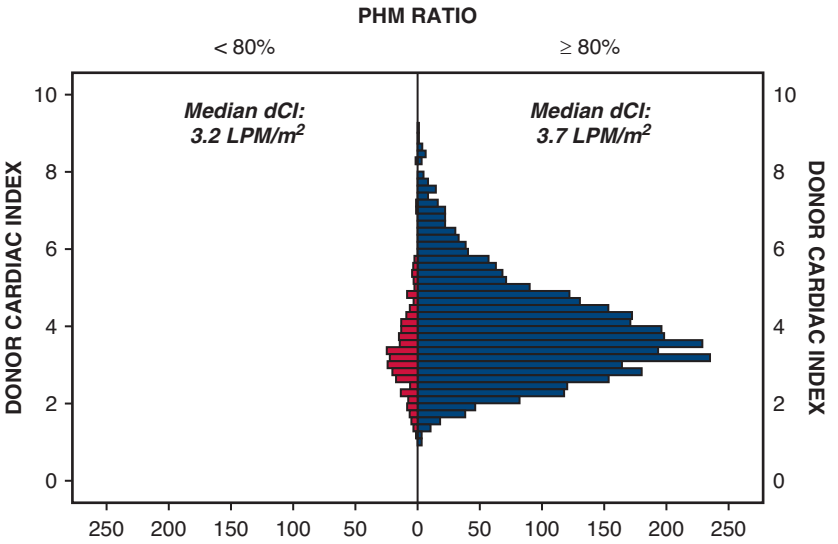

FIGURE E2. Histogram of dCI values for recipients with PHMr less than 80% versus 80% or more. *PHM*, Predicted heart mass; *dCI*, donor cardiac index; *LPM*, liters per minute.

TABLE E1. Univariate association between donor cardiac index (per 1 liter per minute/m2) and outcomes

Outcome	Univariate OR	95% CI	*P* value
Acute rejection	0.97	0.90-1.04	.412
Cerebrovascular accident	1.01	0.88-1.17	.878
Permanent pacemaker	0.96	0.82-1.13	.619
Postoperative dialysis	0.95	0.87-1.03	.186
1-y rejection	0.98	0.91-1.05	.587
1-y mortality	0.91	0.84-0.99	.031
5-y mortality	0.92	0.86-0.98	.012

OR, Odds ratio; *CI*, confidence interval.

TABLE E2. Univariate associations between predicted heart mass ratio and outcomes

Outcome	Univariate OR	95% CI	*P* value
Acute rejection	0.98	0.60-1.61	.934
Cerebrovascular accident	2.42	0.93-6.26	.070
Permanent pacemaker	1.08	0.36-3.27	.895
Postoperative dialysis	0.50	0.28-0.91	.024
1-y rejection	1.03	0.63-1.70	.899
1-y mortality	0.58	0.32-1.03	.066
5-y mortality	0.83	0.53-1.28	.392

OR, Odds ratio; *CI*, confidence interval.

TABLE E3. Multivariable logistic regression model to assess the relationship between predicted heart mass ratio and 1-year mortality

Variable	OR	95% CI	*P* value
Recipient age, y	1.02	1.01-1.03	<.001
Female recipient	1.33	1.02-1.74	.039
Recipient hospitalized	1.45	1.17-1.79	<.001
Preoperative LVAD	1.23	0.99-1.53	.063
Donor inotropes	1.15	0.93-1.42	.190
PHMr	0.43	0.22-0.82	.011

OR, Odds ratio; *CI*, confidence interval; *LVAD*, left ventricular assist device; *PHMr*, predicted heart mass ratio.

TABLE E4. Recipient and donor characteristics for those with and without right heart catheterization

Characteristics	dCI cohort (n = 3615)	No dCI cohort (n = 66,485)	*P* value
Recipient characteristics			
Age (y)	56 (46-62)	55 (46-61)	<.001
Female sex	847 (23)	16,030 (24)	.351
PHM (g)	184 (160-205)	182 (157-202)	<.001
Weight (kg)	82 (70-94)	80 (68-92)	<.001
Height (m)	1.8 (1.7-1.8)	1.8 (1.7-1.8)	.035
BMI (kg/m^2)	27 (24-30)	26 (23-30)	<.001
BSA (m^2)	2.0 (1.8-2.2)	2.0 (1.8-2.1)	<.001
Creatinine (mg/dL)	1.2 (1.0-1.5)	1.2 (1.0-1.5)	.546
PA systolic pressure (mm Hg)	40 (31-50)	40 (31-51)	.134
Pulmonary vascular resistance (Wood units)	(n = 2702) 2.3 (1.7-3.2)	(n = 40,698) 2.4 (1.7-3.3)	.119
Diagnosis			<.001
Dilated cardiomyopathy	2969 (82)	47,943 (72)	
Ischemic cardiomyopathy	250 (7)	10,675 (16)	
Restrictive cardiomyopathy	102 (3)	1520 (2)	
Congenital	78 (2)	1829 (3)	
Other	216 (6)	4382 (7)	
MCS at transplant			<.001
None	2228 (62)	24,233 (59)	
LVAD	1190 (33)	12,300 (30)	
RVAD/BiVAD/TAH ("all others")	197 (5)	4412 (11)	
Donor characteristics			
Age (y)	35 (24-45)	29 (21-40)	<.001
Female sex	1054 (29)	19,522 (29)	.790
PHM (g)	186 (162-207)	183 (159-203)	<.001
Weight (kg)	81 (70-94)	77 (68-90)	<.001
Height (m)	1.8 (1.7-1.8)	1.8 (1.7-1.8)	.771
BMI (kg/m^2)	27 (23-30)	25 (23-29)	<.001
Transplant characteristics			
Ischemic time (h)	3.3 (2.6-3.9)	3.0 (2.3-3.7)	<.001
Female donor to male recipient	571 (16)	10,765 (16)	.529

Data presented as n (%) or median (IQR). *dCI*, Donor cardiac index; *PHM*, predicted heart mass; *BMI*, body mass index; *BSA*, body surface area; *PA*, pulmonary artery; *MCS*, mechanical circulatory support; *RVAD*, right ventricular assist device; *BiVAD*, biventricular assist device; *LVAD*, left ventricular assist device; *TAH*, total artificial heart.