

# Increased Mortality at Low-Volume Orthotopic Heart Transplantation Centers: Should Current Standards Change?

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**Background.** The Centers for Medicare and Medicaid Services (CMS) mandate that orthotopic heart transplantation (OHT) centers perform 10 transplants per year to qualify for funding. We sought to determine whether this cutoff is meaningful and establish recommendations for optimal center volume using the United Network for Organ Sharing (UNOS) registry.

**Methods.** We reviewed UNOS data (years 1999 to 2006) identifying 14,401 first-time adult OHTs conducted at 143 centers. Stratification was by mean annual institution volume. Primary outcomes of 30-day and 1-year mortality were assessed by multivariable logistic regression (adjusted for comorbidities and risk factors for death). Sequential volume cutoffs were examined to determine if current CMS standards are optimal. Pseudo  $R^2$  and area under the receiver operating curve assessed goodness of fit.

**Results.** Mean annual volume ranged from 1 to 90. One-year mortality was 12.6% ( $n = 1,800$ ). Increased center volume was associated with decreased 30-day mortality ( $p < 0.001$ ). Decreased center volume was associated with increases in 30-day (odds ratio [OR] 1.03, 95% confidence interval [CI]: 1.02 to 1.03,  $p < 0.001$ ) and 1-year mortality (OR 1.01, 95% CI: 1.01 to 1.02,  $p =$

0.03—censored for 30-day death). The greatest mortality risk occurred at very low volume centers ( $\leq 2$  cases = 2.15 times increase in death,  $p = 0.03$ ). Annual institutional volume of fewer than 10 cases per year increased 30-day mortality by more than 100% (OR 2.02, 95% CI: 1.46 to 2.80,  $p < 0.001$ ) and each decrease in mean center volume by one case per year increased the odds of 30-day mortality by 2% (OR 1.02, 95% CI: 1.01 to 1.03,  $p < 0.001$ ). Additionally, centers performing fewer than 10 OHTs per year had increased cumulative mortality by Cox proportional hazards regression (hazard ratio 1.35, 95% CI: 1.14 to 1.60,  $p < 0.001$ ). Sequential multivariable analyses suggested that current CMS standards may not be optimal, as all centers performing more than 40 transplants per year demonstrated less than 5% 30-day mortality.

**Conclusions.** Annual center volume is an independent predictor of short-term mortality in OHT. These data support reevaluation of the current CMS volume cutoff for OHT, as high-volume centers achieve lower mortality.

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More than 45 years have passed since Norman Shumway and Richard Lower described the initial technique for orthotopic heart transplantation (OHT) [1]. When OHT was first applied to humans, only certain centers with specially trained surgeons and substantial resources could undertake the procedure and care for the complex posttransplant patient. As time has passed with improvements in immunosuppression, intensive care unit care, organ preservation, and surgical technique, OHT has evolved to become the gold standard treatment for a variety of types of end-stage heart disease and is avail-

able in many centers worldwide. With more than 140 centers performing OHT in the United States alone, a wide disparity exists in the number of cases performed between centers. Because many procedures have volume-based outcomes, a similar analysis asking if center volume correlates with outcomes in OHT should be performed.

Hospital volume has been shown to affect surgical outcomes for many types of surgery. In fact, over the past 30 years, several studies (examining pancreatic resections, esophagectomies, lung lobectomies, and so forth) have convincingly demonstrated that increased provider volume is correlated with lower mortality [2–9], shorter length of hospital stay [10], decreased readmission rates [11], and decreased costs [10, 12, 13]. This concept is not only pervasive in general surgery but has also found its way into specialty surgical fields as well including urol-

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ogy [14], gynecology [15, 16], and vascular [17] and cardiovascular surgery [18–20]. These findings have been advocated by health quality consortiums, such as the Leapfrog Group, and discussed in the lay press [21].

The volume-outcome relationship appears to be particularly important for highly complex procedures that require a significant commitment of resources and highly specialized teams [22]. Orthotopic heart transplantation is a clear example of this type of procedure. In fact, several studies have demonstrated a center effect whereby low-volume OHT centers have increased short-term mortality rates [23–25].

In response to this early work and the growing success of OHT after the advent of cyclosporine, the Health Care Financing Administration (HCFA)—whose name was changed in 2001 to the Centers for Medicare and Medicaid services (CMS)—publicly decided in 1986 that Medicare would fund OHT at HCFA-designated institutions that met strict outcome standards and performed a minimum volume of transplantations per year. Initially, this minimum number was set at 12 cases per year. Current CMS standards require only 10 cases per year for approval [26].

It has now been 20 years since this initial mandate, and although the importance of center volume appears clear, most studies addressing this issue for OHT were conducted in the late 1980s and early 1990s, before advances in immunosuppressive and myocardial protection and support gained significant acceptance. Furthermore, no study has been designed to specifically examine CMS standards directly.

The United Network for Organ Sharing (UNOS) dataset is a nation-wide, physician-overseen sample that provides a unique opportunity to address the issue of center volume while minimizing single-institution bias. We conducted a retrospective examination of the multi-institutional UNOS dataset to examine effects of annual institutional volume on short-term and midterm survival in patients receiving OHT. We hypothesize that increased center volume will be associated with decreased short-term mortality independent of patient risk factors,

and further, that the current CMS standard may not be optimal.

## Material and Methods

### Data Source

The UNOS provided deidentified patient data (standard transplant analysis and research [STAR] files) from the Thoracic Organ Transplant Registry for the years of 1987 to 2006, with follow-up through September of 2007. Unique center identifier codes were included to allow examination of institutional volume. The data include 433 unique demographic, operative, and postoperative variables collected for all United States patients undergoing thoracic organ transplantation and reported to the Organ Procurement Network during the time period. As individual patients are not identified in this multicenter registry report, the need for consent and Institutional Review Board approval is waived at our institution.

### Study Design and Patient Population

A retrospective review of the UNOS dataset from January 1999 to December 2006 with follow-up through January 2007 was performed. These time points were chosen to identify a modern cohort of patients who underwent OHT with current management techniques. All first-time orthotopic heart transplant patients between 18 and 80 years of age were included.

### Institutional Volume

Using the unique center identifiers present in the UNOS dataset, the variable of annual institutional volume was derived from the extant data. In this way, each individual patient outcome was linked to a hospital volume measurement. We then primarily stratified by volume to “low-volume centers” (performing fewer than 10 OHTs per year) and “high-volume centers” (performing 10 or more OHTs per year). To further assess the effects of volume for centers with either very low or very high volume, additional volume cutoffs were defined and

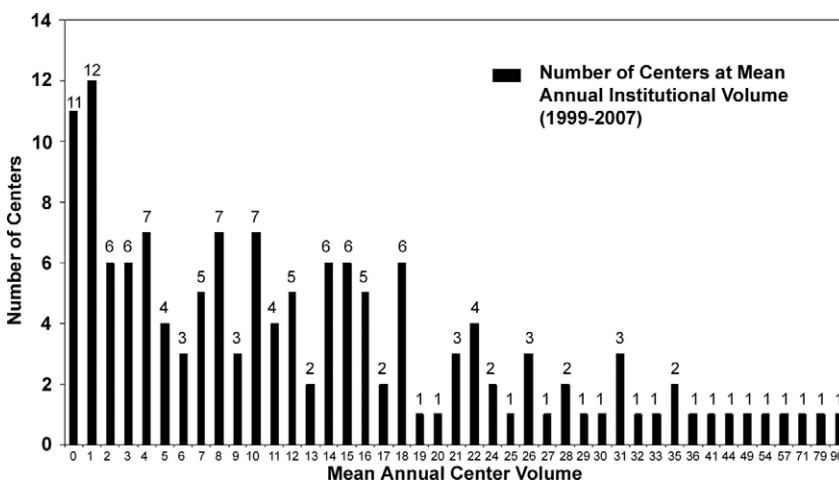


Fig 1. Distribution of center volumes for 143 centers included in the United Network for Organ Sharing dataset. Sixty-four centers fall below the requirement for Centers for Medicare and Medicaid Services funding of 10 orthotopic heart transplantations per year (based on Organ Procurement and Transplantation Network data, January 2007).

Table 1. Baseline Characteristics of Patients Undergoing Orthotopic Heart Transplantation (OHT) at Low-Volume (< 10 OHT per Year) Versus High-Volume (≥ 10 OHT per Year) Centers

	Low Volume (< 10 OHT/Year) n = 1,608 No. (%) or Mean (SD)	High Volume (≥ 10 OHT/Year) n = 12,793 No. (%) or Mean (SD)	p Value <sup>a</sup>
<b>Demographics</b>			
Mean center volume	5.9 (2.4)	33.2 (22.0)	< 0.001
Mean age, years	49.8 (12.8)	52.2 (11.8)	< 0.001
Age ≥ 65 years	6.7 (108)	11.9 (1529)	< 0.001
Female	377 (23.4)	3,054 (23.8)	0.75
Black, Hispanic, Native American, Asian/Pacific Islander <sup>b</sup>	426 (26.5)	3,091 (24.1)	0.04
<b>Comorbidities and acuity</b>			
History of hypertension	600 (39.2)	4,858 (39.7)	0.29
Diabetes mellitus	311 (19.6)	2,689 (22.5)	0.08
Preoperative creatinine	1.4 (0.9)	1.4 (0.8)	0.8
Body mass index	26.4 (4.9)	26.4 (4.7)	0.84
Hospitalized before transplant	810 (51.6)	6,469 (51.1)	0.76
ICU before transplant	437 (27.8)	3,934 (31.1)	0.01
IABP before transplant	66 (4.1)	687 (5.3)	0.03
Inotropes before transplant	557 (36)	5,388 (46)	< 0.001
Ventilated before transplant	56 (3.5)	362 (2.8)	0.14
UNOS status 1 <sup>c</sup>	1,166 (72.5)	9,501 (74.3)	0.12
Days on wait list	239 (391)	223 (371)	0.1
Bicaval anastomosis	484 (31.7)	5,807 (48.0)	< 0.001
Donor age (years)	31.1 (12.4)	31.6 (12.6)	0.14
Ischemic time (hours)	3.04 (1)	3.15 (1)	<0.001
<b>Hemodynamic variables</b>			
Mean pulmonary artery pressure	28.1 (10.4)	28.4 (10.0)	0.06
Pulmonary vascular resistance <sup>d</sup>	2.2 (2)	2.4 (2)	0.07
Cardiac index	2.3 (0.8)	2.3 (0.8)	0.61
Transpulmonary gradient <sup>e</sup>	9.0 (6.3)	9.5 (5.6)	0.01

<sup>a</sup> The p value is based on comparison between two groups by either  $\chi^2$  or Student's *t* test. <sup>b</sup> Both race and ethnicity were variables present in the dataset. <sup>c</sup> UNOS status 1 refers to patients listed as status 1a, status 1b, or older UNOS status 1. <sup>d</sup> Pulmonary vascular resistance defined by mean pulmonary artery pressure minus pulmonary capillary wedge pressure divided by cardiac output. <sup>e</sup> Transpulmonary gradient defined by mean pulmonary artery pressure minus pulmonary capillary wedge pressure.

IABP = intra-aortic balloon pump; ICU = intensive care unit; UNOS = United Network for Organ Sharing.

included fewer than 2, fewer than 5, 5 to 9, 10 to 40, and more than 40 OHTs per year.

*Variables Examined and Measures of Outcome*

Of the 433 variables present in the UNOS dataset, pertinent clinical factors were compared between groups. Specifically studied were baseline recipient demographic factors (age, sex, and race), comorbidities (hypertension, diabetes mellitus, body mass index, and preoperative creatinine levels), and transplant variables (donor age, ischemic time, anastomotic technique, human leukocyte antigen mismatch, and year of transplant). In addition, we examined markers of clinical acuity including whether the patient was hospitalized or in an intensive care unit before transplant, use of intra-aortic balloon counterpulsation before transplant, and UNOS status. Finally, hemodynamic variables before transplant were identified, including mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, and transpulmonary gradient. The primary endpoint was

30-day mortality. Other endpoints included 1-year and cumulative mortality.

*Analysis*

Comparisons of baseline characteristics between study groups were performed using Student's *t* test for continuous variables and the chi-square test for categorical variables. Cumulative survival was modeled using the Kaplan-Meier method, with statistical differences between survival curves assessed by use of the log-rank (Mantel-Cox) test. In addition, modeling based on 1-year conditional survival was employed to assess long-term survival independent of early mortality. Mortality was first assessed for all risk factors using a univariate model. Analysis was conducted by use of multivariable logistic regression for short-term (30-day and 1-year) mortality and by use of a Cox proportional hazards regression model for cumulative mortality. Significant univariate predictors of either short-term or cumulative mortality were incorporated into the multivariable model to assess the effect of volume on

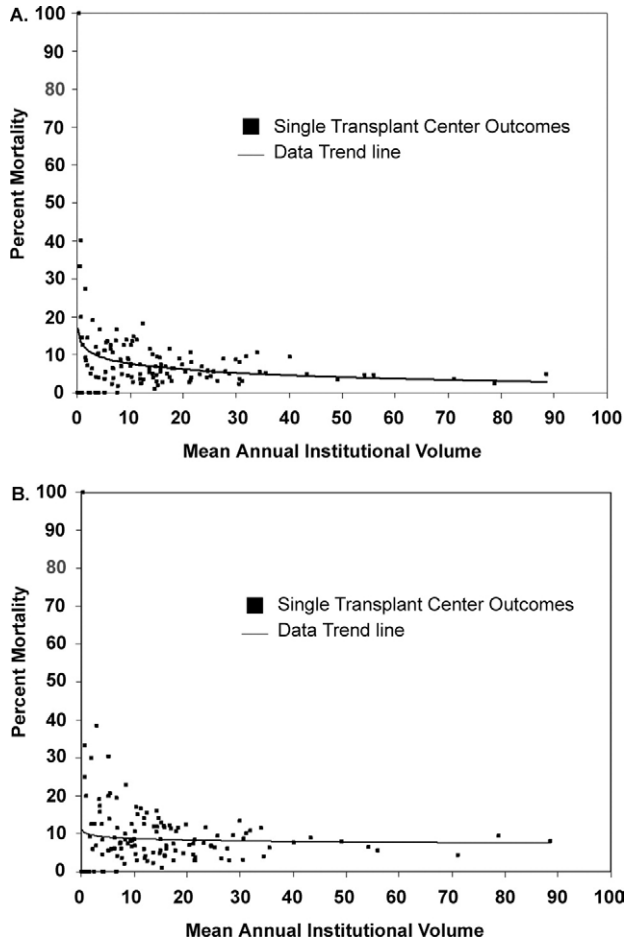


Fig 2. Individual center unadjusted percent mortality as plotted by mean annual center orthotopic heart transplantation volume. Both (A) 30-day and (B) 1-year mortality censored for 30-day mortality are included. Data trend lines are provided, demonstrating the substantial effect that center volume has on 30-day mortality (based on Organ Procurement and Transplantation Network data, January 2007).

mortality. Only well-represented variables (less than 33% missing in the registry) were included in multivariable analysis.

To determine if the current CMS standard of 10 OHTs per year is optimal, we performed a series of sequential multivariable logistic regressions at changing volume thresholds examining 30-day mortality as an endpoint. Common independent variables (significant on univariate analysis) were included along with the sequentially changing independent variable of dichotomized annual OHT volume. This allows for comparison of outcomes from hospitals with less than versus those with greater than or equal to, the changing volume cutoff. To illustrate this concept, the first multivariable regression compared centers with a mean annual center volume of 1 or more and centers performing a mean of fewer than 1 per year. The second regression compared those at a mean annual center volume of 2 or more with those averaging fewer than 2 per year. Sequential analyses were performed in

this manner until a volume threshold was tested for all center volumes. Various measures of “goodness of fit” were used examined for each comparison. These included area under the receiver operating curve (AUC) and McFadden’s Pseudo  $R^2$  [27–29]. The latter result is normalized and presented as a percentage.

For all analyses, a  $p$  value of less than 0.05 (two-tailed) was considered significant, and all odds ratios (OR) and regression coefficients are presented with 95% confidence intervals (CI). All statistical analysis was performed with the aid of STATA software (version 9.2; StataCorp LP, College Station, Texas).

## Results

During the 8-year study period, UNOS data revealed 143 unique OHT centers, ranging in mean annual institutional volume from 1 to 90 cases per year, with a median volume

Table 2. Multivariable Logistic Regression Model for 30-Day Mortality

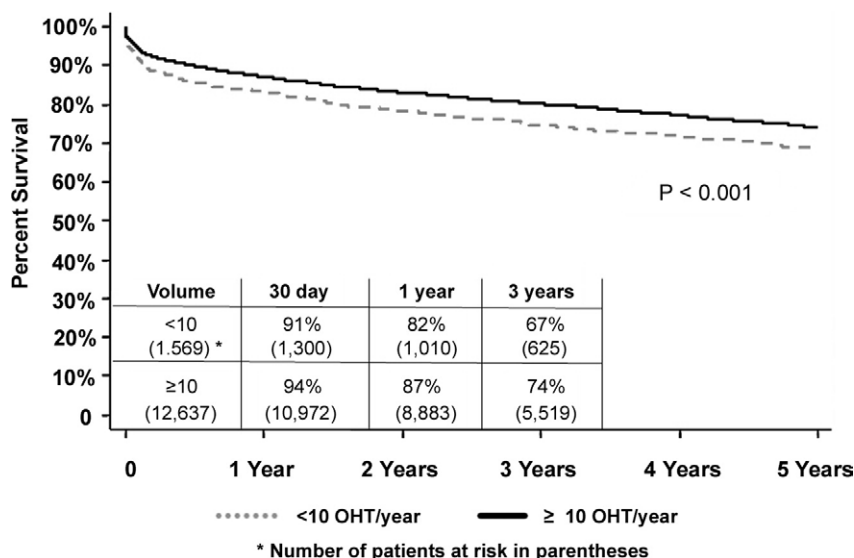
Risk Factor	OR (95% CI)	$p$ Value <sup>a</sup>
Volume (continuous)	0.97 (0.97–0.98)	< 0.001
Volume < 10 <sup>b</sup>	2.02 (1.46–2.80)	< 0.001
Volume < 5	1.86 (1.04–3.32)	0.04
Volume ≤ 2	2.15 (1.02–4.56)	0.03
Volume < 2	1.66 (0.38–7.2)	0.48
Volume ≥ 40	0.35 (0.22–0.56)	< 0.001
Age	1.01 (1.00–1.02)	0.14
Sex (female versus male)	0.84 (0.62–1.14)	0.26
Hypertension	1.32 (1.02–1.71)	0.03
Diabetes mellitus	0.86 (0.63–1.18)	0.35
Creatinine	1.20 (1.11–1.30)	< 0.001
Panel reactive antibody (continuous)	1.01 (0.99–1.01)	0.14
UNOS status 1	1.87 (1.30–2.69)	0.001
Donor age	1.01 (1.0–1.02)	0.05
HLA mismatch (HLA ≤ 4 versus 5 or 6)	0.87 (0.67–1.12)	0.27
Ischemic time	1.27 (1.14–1.43)	< 0.001
Cardiac index	0.95 (0.74–1.21)	0.70
Pulmonary vascular resistance	1.04 (0.97–1.10)	0.2
Bicaval anastomosis	0.93 (0.70–1.23)	0.61
Mechanical ventilation before transplant	4.33 (2.56–7.33)	< 0.001
Intensive care unit before transplant	0.98 (0.71–1.34)	0.9
Transplantation year	0.90 (0.83–0.98)	0.02

<sup>a</sup> The  $p$  value is based on multivariable logistic regression analysis, using factors significant on univariate analysis. <sup>b</sup> Volume defined as mean number of OHT cases/year.

Multivariable model included the following variables: mean annual center orthotopic heart transplant (OHT) volume (continuous), age, sex, history of hypertension, history of diabetes mellitus, preoperative creatinine, panel reactive antibody level, UNOS status 1, donor age, HLA mismatch, ischemic time, preoperative cardiac index, preoperative pulmonary vascular resistance, bicaval anastomotic technique, need for mechanical ventilation before undergoing transplantation, and transplantation year.

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio; UNOS = United Network for Organ Sharing.

Fig 3. Kaplan-Meier estimates of 5-year survival for patients who underwent orthotopic heart transplantation (OHT) at high-volume (black line) and low-volume (gray dashed line) centers. A survival table is provided, and the number of patients at risk is given in parentheses. The *p* value corresponds to Mantel-Cox log-rank test results (based on Organ Procurement and Transplantation Network data, January 2007).



of 10 cases a year (Fig 1). At these 143 centers, 17,131 patients underwent OHT, and after exclusion of patients with previous heart transplant (*n* = 601) and patients less than 18 years of age (*n* = 2,128), 14,401 patients were included in the final analysis.

Primary stratification revealed that 11% (*n* = 1,608) of patients received OHT at centers performing an average of fewer than 10 transplants per year (64 centers = 45%). An additional 31 centers, who averaged 10 or more OHTs per year, failed to achieve 10 transplants in at least 1 year of the study. Thus, the total number of centers failing to achieve at least 10 OHTs in all 8 years of the study was 95 (66%).

#### Baseline Demographics and Acuity

Patients transplanted at low- and high-volume centers differed slightly in their baseline characteristics (Table 1). Sex was equally distributed, although high-volume centers had a slightly greater number of underrepresented minorities and transplanted patients who were slightly older. In addition, patients at low- and high-volume centers had similar rates of comorbidities, including hypertension and diabetes mellitus. High-volume cen-

ters appeared to have slightly higher levels of acuity as assessed by rates of intensive care unit admission, inotrope use, and intra-aortic balloon pump before transplant. Rates of hospitalization before transplantation and rates of listing as UNOS status 1, however, were similar between groups. Hemodynamic variables were also similar between groups. High-volume centers did have a higher rate of performing OHT with the bicaval anastomotic technique, which may reflect that increased experience is necessary for proficiency with the multiple anastomoses.

#### Center Volume and Unadjusted Mortality

During the study period, cumulative mortality was 21%, with a 30-day mortality rate of 6%. Thirty-day and 1-year mortality were both higher at low-volume centers on unadjusted analysis: 8.5% versus 5.6% (*p* < 0.001), and 16.2% versus 12.2% (*p* < 0.001), respectively. Upon additional stratification, very low volume centers (fewer than 5 cases per year on average) demonstrated an unadjusted 30-day mortality rate of 9.2%, and those performing 0 to 1 transplants per year on average had a 30-day mortality

Fig 4. Kaplan-Meier estimates of 5-year survival censored for patients who died before 1-year follow-up and stratified by mean center volume. A total of 10,347 patients survived beyond 1 year. The only group that varied significantly from others was those centers performing 5 or fewer OHTs per year. \**p* < 0.001 for this volume group when compared with the others using the Mantel-Cox log-rank test (based on Organ Procurement and Transplantation Network data, January 2007).

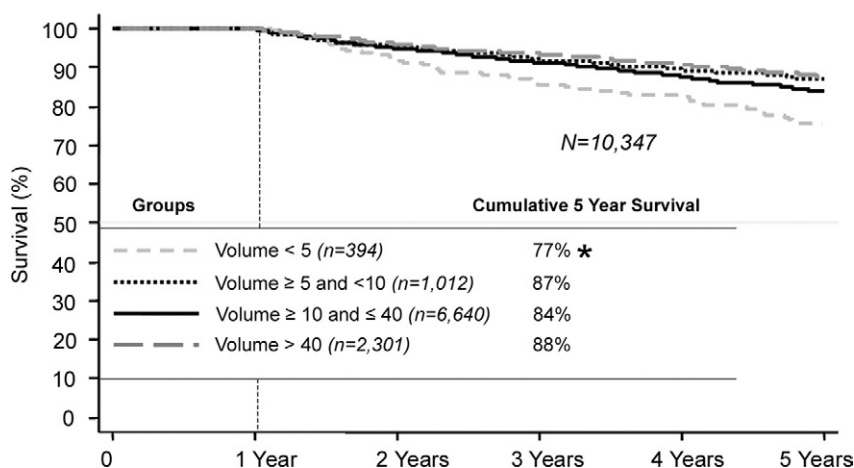


Table 3. Multivariable Cox Proportional Hazards Regression Model for Cumulative Mortality

Risk Factor	HR (95% CI)	p Value <sup>a</sup>
Volume (continuous)	0.99 (0.98-0.99)	<0.001
Volume < 10 <sup>b</sup>	1.35 (1.14-1.60)	<0.001
Volume < 5	1.90 (1.45-2.51)	<0.001
Volume ≤ 2	1.78 (1.08-2.86)	0.02
Volume < 2	1.73 (0.89-3.40)	0.1
Volume ≥ 40	0.71 (0.59-0.85)	<0.001

<sup>a</sup> The p value is based on multivariable Cox proportional hazards regression analysis, using factors significant on univariate analysis. <sup>b</sup> Volume defined as mean number of OHT cases per year.

Multivariable model included the following variables: mean annual center orthotopic heart transplant (OHT) volume (continuous), age, sex, history of hypertension, history of diabetes mellitus, preoperative creatinine, panel reactive antibody level, UNOS status 1, donor age, human leukocyte antigen mismatch, ischemic time, preoperative cardiac index, preoperative pulmonary vascular resistance, bicaval anastomotic technique, need for mechanical ventilation before undergoing transplantation, and transplantation year. Additional significant predictors of cumulative mortality include history of diabetes, history of hypertension, panel reactive antibody level (continuous), creatinine, mechanical ventilation before transplant, donor age, and ischemic time. Transplant year and UNOS status 1 did not emerge as significant predictors of cumulative mortality but were predictors of 30-day mortality (Table 2).

CI = confidence interval; HR = hazard ratio; UNOS = United Network for Organ Sharing.

of 15.2% (Fig 2). One-year mortality rates were also increased at very low volume centers (18.2% versus 12.4%,  $p < 0.001$ , for centers performing fewer than 5 OHT per year compared with 5 or more per year (22% versus 12.6%,  $p < 0.001$ , for centers performing 0 to 1 OHT per year compared with 2 or more per year). It is noteworthy that all centers performing more than 40 OHTs per year demonstrated less than 5% 30-day mortality (Fig 2).

Multivariable Analysis

On multivariable analysis, decreased center volume was significantly associated with an increase in short-term mortality. Specifically, each decrease in mean center volume by 1 case per year increased the odds of 30-day

mortality by 2% (OR 1.02, 95% CI: 1.01 to 1.03,  $p < 0.001$ ). In addition, falling below the CMS standard of 10 cases per year led to a 100% increase in risk of 30-day mortality (Table 2). Other significant predictors of death on multivariable logistic regression included ischemic time, baseline creatinine level, hypertension, transplantation year, listing as UNOS status 1, donor age, and the requirement of mechanical ventilation before transplantation (Table 2). Centers performing fewer than 5 OHTs per year and those performing 2 or fewer OHTs per year also had significant increases in the odds of 30-day mortality on multivariable logistic regression. Performing more than 40 OHTs per year was associated with a 65% decrease in the odds of 30-day mortality. The effect of volume was not restricted to 30-day mortality, as logistic regression of 1-year mortality censored for 30-day death revealed increased mortality for low-volume centers (OR for death at low-volume [ $< 10$  OHT per year] centers = 1.50, 95% CI: 1.06 to 2.02,  $p = 0.02$ ).

Cumulative Survival

Unadjusted cumulative survival was first evaluated by the Kaplan-Meier method. Although cumulative survival was lower at centers performing fewer than 10 cases per year (Fig 3), censoring for 1-year mortality eliminated the effect, indicating that differences in long-term survival for those centers performing fewer than 10 OHTs per year are largely related to increases in early mortality (Fig 4). Upon further stratification, however, those centers performing fewer than 5 OHTs per year did show a significant difference in cumulative Kaplan-Meier survival even after censoring for 1-year mortality ( $p < 0.001$ ). High-volume centers (more than 40 OHTs per year) did not show a cumulative survival benefit when censored for early death. On Cox proportional hazards regression analysis, however, low-volume center status (fewer than 10 OHTs per year) was associated with a significant increase in cumulative mortality (hazard ratio = 1.35, 95% CI: 1.14 to 1.60,  $p < 0.001$ ) when compared with high-volume centers (10 or more OHTs per year). In addition, centers performing fewer than 5 OHTs per year

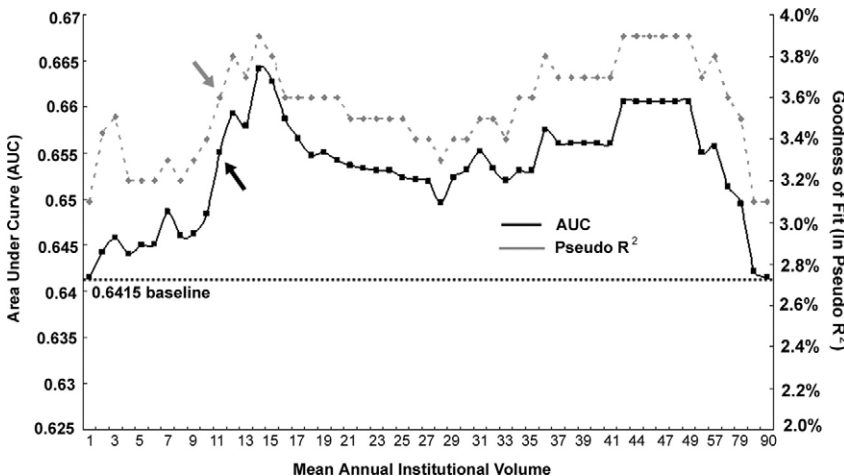


Fig 5. Various models of goodness of fit: area under the receiver operating curve (AUC [black]) and McFadden's pseudo R<sup>2</sup> as a percentage (gray) of the sequential multiple logistic regression analyses performed at sequential volume cutoffs. Black and gray arrows point to goodness of fit for comparison between centers performing 10 or more cases per year versus fewer than 10 cases per year. This plot demonstrates that the current Centers for Medicare and Medicaid Services standard of 10 OHTs per year was not the optimal fit in this model. The dotted line represents the baseline AUC for the model with no volume variable, which was 0.6415.

and those performing 2 or fewer OHTs per year had significantly lower cumulative survival when compared with higher volume centers (Table 3).

### *Optimal Center Volume*

Sequential multivariable logistic regressions at changing volume thresholds were conducted, examining 30-day mortality as an endpoint. At each sequential volume threshold, low-volume centers were associated with a significantly increased risk of adjusted 30-day mortality when compared with higher volume centers. The goodness of fit of the sequential models as assessed by the AUC varied from a nadir of 0.64 to a maximum of 0.665. Performing more than 10 cases per year led to an AUC of 0.6551, which did not account for the greatest variability in the model, and thus indicates that achieving a volume of 10 does not predict mortality with highest accuracy in our multivariable analysis. The results of the McFadden Pseudo  $R^2$  mirrored that of the AUC calculations (Fig 5).

### **Comment**

In our analysis of cardiac transplant centers, we confirm that a reduced volume of OHTs is associated with an increase in short-term mortality. Our intention was to provide a thorough treatise on the “center effect” in OHT and determine whether current CMS standards are indeed appropriate. The large multi-institutional UNOS dataset was used to provide an account of the effect of volume on OHT during the years 1999 to 2006 to focus on outcomes unaffected by major advances in the field of heart transplantation. The CMS-defined cutoff of 10 has been criticized by some as being too small. However, it is noteworthy that despite this volume threshold being required by CMS to receive federal funding, 65% of centers studied failed to achieve this level during at least one year of the study period.

The data provided in this analysis clearly point to a volume effect whereby increased center volume leads to a reduction in short-term mortality. This effect is most pronounced at low-volume centers performing fewer than 10 OHTs per year, as these low-volume centers have a 100% increase in the risk of 30-day mortality when compared with centers performing at least 10 OHTs per year. It is also clear that having an OHT at a center performing 2 or fewer OHTs per year is associated with a 115% increase in 30-day mortality. Some individual very low volume centers have alarmingly high 30-day mortality rates. For example, there were five centers performing an average of fewer than 1 OHT per year that demonstrated 30-day mortality rates of more than 20%. Conversely, achieving high volumes was associated with superior outcomes. All centers performing more than 40 OHTs per year demonstrated less than 5% 30-day unadjusted mortality. Furthermore, it is clear that substantial intercenter variance is reduced once a volume of 20 OHTs per year is achieved.

It is important to note that not all low-volume centers have poor outcomes, and there is not a level of OHT

volume that ensures a superior outcome. Thirteen centers that averaged fewer than 1 OHT per year demonstrated a 0% 30-day mortality rate. These data support the concept that increased institutional experience and activity is one factor associated with improved OHT outcomes.

It is noteworthy that high-volume centers had improved outcomes despite arguably increased acuity (as measured by greater number of patients in an intensive care unit before transplantation and preoperative intra-aortic balloon pump and inotrope use). Furthermore, high-volume centers transplanted a greater number of older patients (older than 65 years). In this analysis, we chose to include all adult patients (up to age 80). We did this to limit biasing the results in favor of improved survival at high-volume institutions (who treat a greater number of older patients). Although age 65 is generally considered a cutoff for performing OHT, a substantial body of evidence now exists supporting acceptable outcomes for older patients who undergo OHT [30]. Although the data are not presented here, exclusion of patients older than age 65 did not alter the results of this analysis.

Although volume effects were most significant for 30-day mortality, long-term survival was also influenced by volume status. One-year mortality was higher for low-volume centers even after censoring for 30-day mortality. Long-term survival proved less dependent on center volume status, as censoring for 1-year mortality led to similar 5-year survival by Kaplan-Meier analysis. This indicates that the majority of low-volume programs have their mortality within the first year. The notable exception to this trend was for centers performing fewer than 5 OHTs per year. These centers demonstrated decreased cumulative survival even with censoring for 1-year mortality. Cox proportional hazards regression also indicated that decreased volume led to increases in cumulative mortality. The reasons for this trend are not apparent from this dataset, but we can speculate that they may relate to processes of care, such as limited resources and expertise needed to appropriately follow complex posttransplant patients at low-volume institutions over time.

### *Importance of Volume in OHT*

In addition to the findings of this study, substantial literature has now provided ample support to the notion that increased center and provider volume is important for improved outcomes after surgical procedures [2–4, 6]. This effect is particularly true for transplantation where patients and procedures are complex, and significant hospital resources are required [22]. Several reports have now confirmed that this “center effect” exists for OHTs as well [23–25]. In two early reports utilizing the International Society of Heart and Lung Transplantation (ISHLT) registry, published by Heck and colleagues [25] and Evans and coworkers [23], low-volume OHT centers demonstrated increased mortality rates. In an early study conducted from 1984 to 1986 and based primarily on survey data, Laffel and colleagues [31] demonstrated that

while volume plays a role in outcome after OHT, the primary factor is the learning curve that takes place, as supported by centers reporting progressively improved outcomes over time.

The importance of this learning curve was refuted in a more recent definitive study by Hosenpud and associates [24] who failed to show improvement in outcomes over the history of a program's experience. This study similarly utilized the UNOS dataset and examined outcomes by center volume from 1987 to 1991. Centers were dichotomized into low (fewer than 9 OHT a year) and high-volume centers (9 or more OHT a year), and 30-day and 1-year survival was lower in the low-volume group. The authors made note of the fact that more than 50% of centers were in the low-volume group.

More than 14 years have passed since this description of the volume effect in OHT, and the currently used definition of high-volume center remains similar. Although we still believe volume to be important, reexamination of this issue in the context of current surgical, immunosuppressive, and critical care advances was warranted.

Volume cutoffs are often arbitrarily defined and not based on strict outcome standards. We attempted to determine whether the current CMS standard of 10 cases per year was indeed the "optimal" volume threshold by analyzing the amount of variability in the data accounted for by this volume cutoff and comparing it to other possible cutoffs. We used sequential statistical modeling centered on volume and compared the resultant "goodness of fit" from each model. Based on this technique, performing 10 OHTs per year did not account for the greatest variability in the model. An important finding from this analysis, however, is that volume differences account for no more than 1% of the variance in the sequential multivariable models. This apparent paradox whereby volume is clearly important but not sufficient to fully explain mortality after OHT highlights the complexity of these patients and underscores the importance of identifying additional factors that affect outcomes beyond volume alone.

#### *Processes of Care*

Thus, the findings of the current and previous studies lead us to speculate that center volume is one factor that is highly important for short-term survival in OHT. This notion, however, must be taken in the context of recent work focusing on institutional factors affecting postoperative outcomes. Many recent studies have focused on "processes of care" that affect outcome, including the presence of dedicated intensive care unit providers [32, 33], implementation of patient safety measures [34], a multidisciplinary team approach, and implementation of critical pathways [5, 35, 36]. Most of this work has been examined using general surgery patients. However, it is likely that these processes of care are equally important for transplantation, where patients are complex and utilize a variety of hospital resources. It is likely that volume may be serving as a surrogate for additional unidentified processes unable to be quantified using the

multi-institutional UNOS dataset. This last point underscores the importance of identifying these unknown processes of care to help improve all centers—local, regional, and national alike—to improve care for heart transplant patients. To what degree of importance surgeon experience affects the outcomes above and beyond these other processes cannot be quantified in this analysis and should be the subject of further study.

#### *Access to Care and Organ Utilization*

Restricting complicated procedures such as OHT to "centers of expertise" may impose unique access to care challenges to patients, families, and payers. This is a potential burden that cannot be ignored. However, it is also noteworthy that high-risk patients are frequently not accepted as recipients at lower volume centers owing to fear of their impact on center mortality results. Access to care is rarely examined from this perspective. However, it is possible that limiting OHT to high-volume centers of expertise may in fact increase access to care for high-risk patients. Furthermore, our review indicates that high-volume centers have better outcomes for high-risk patients.

Organ utilization may also be improved by limiting OHT to high-volume centers. Low-volume centers are less likely to accept "marginal" donors owing to the same mortality concerns mentioned and are therefore less likely to have a listed recipient appropriate and available for any given donor. For these reasons, discussion of limiting OHT to centers of expertise must also include mention of these important issues of access to care as well as organ utilization.

#### *Limitations*

As in all retrospective studies, this analysis has limitations. The UNOS database provides limited variables. Had other variables been included in this database, the observed results may have been different. Specifically, the UNOS dataset offers limited information on immunosuppressive regimens, type of rejection, and processes of care already mentioned. Furthermore, follow-up is limited. This study is retrospective and, by nature, cannot account for inherent undocumented differences in patient characteristics. Although multivariable analysis partially controls for this bias, one fundamental limitation of any retrospective study is a lack of control of all potential patient confounders. Nationwide clinical registries, including the UNOS database, rely upon accurate coding of information. We acknowledge that the data present may not have necessarily been entered by individuals with clinical expertise, and it is further unknown if errors were made in the coding of information. However, errors of this nature are likely to be equally distributed throughout the data and should not lead to significant bias in the results. Finally, from a mathematical perspective, it is difficult to draw strong conclusions about outcomes at centers with very low volume. Despite the size of the dataset, centers performing fewer than 1 OHT per year will have variable outcomes that are difficult to compare. It is difficult to know whether a high mortality rate at a

low-volume center is due to natural variance or a clear trend.

In conclusion, low-volume cardiac transplantation is correlated with increased mortality. Furthermore, 45% of UNOS centers fall below CMS standards, performing an average of fewer than 10 OHTs per year. These findings should reinforce the notion that center volume, whether by itself of serving as a surrogate for processes of care, is important for improved outcomes after OHT. They should also lead to the reevaluation of the current CMS volume cutoff of 10 OHTs per year. Appropriate evidence-based volume standards should be established from multi-institutional data and active consideration of enforceable penalties should exist for centers repeatedly falling below acceptable levels.

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## DISCUSSION

**DR NICHOLAS G. SMEDIRA** (Cleveland, OH): Mister Chairman, members of the Society, and guests. Dr Weiss, I enjoyed your presentation and I enjoyed reading your concise, extremely well written, and what I am sure will be an extremely controversial manuscript. And before I ask a few questions and make a final comment, I would like to recognize Dr Weiss for his impressive accomplishments.

Dr Weiss obtained his medical degree from and completed his general surgery training at Johns Hopkins University, and since 2006 he has been the Irene Piccinini Investigator in cardiac surgery, completing the investigation we just saw and two other investigations, one on cystic fibrosis, which will be presented at IHLST, as the lead author, and another one at the American Association for Thoracic Surgery. Doctor Weiss, congratulations on your productivity.

Let me focus on the two concerns about outcome assessments, both of which we heard about in the first talk this morning, and these are risk adjustment for patient characteristics and the high variability in outcomes among low-volume centers.

Let's look at risk adjustment. It appears from the data that patients in the low-volume centers were at lower risk: they were younger, fewer intensive care unit patients, fewer intra-aortic balloon pumps were used. However, some variables that I am familiar with that impact transplant risk such as active use of short- or long-term mechanical circulatory support or an underlying diagnosis of congenital heart disease did not appear to be validated. How confident are you that the UNOS data provided valid and accurate information for risk assessment?

It is known, as was discussed earlier, that patient risk factors directly impact complication rates, failure to rescue from complications, and mortality. However, hospital characteristics such as high nurse-to-bed ratios, the presence of residents or a teaching facility, and large hospital size show a divergence, with more complications but better recovery from complications and lower mortality. To help us understand the mechanism for higher mortality at low-volume centers, have you thought of and could you incorporate hospital characteristics or, as you call them, "processes of care," into your model?

Let's focus on variability. As you noted, there is huge variability in outcomes in low-volume centers. This was shown in your talk and the paper. There are many low-volume centers with outstanding results. As you propose these regulatory changes, we must keep in perspective that only 10% of the transplants done were at low-volume centers and nearly 50% of centers would have fit the low-volume criteria. How will you respond to the angry words of the low-volume centers with consistently good or great results when we shut them down for failing to meet the 10 or 14 patients per year requirement, and can you foresee any unanticipated consequences, as I can, such as listing patients that might not necessarily need to be listed just to fill the list or performing a transplant just meet numbers?

You take great effort to find a scientific way to determine minimum center volume and recommend going from 10 to 14 based on a 0.2 difference in the C-value. In general, a C-value of greater than 0.7 is needed for a good fit. You don't give confidence intervals for your C-statistic. Can you justify statistically the recommendation that intuitively looks a little bit

silly—increasing the requirement from 10 to 14 transplants per year?

And finally, I will leave you with my thoughts. I agree in principle with your thesis and think very low volume centers should be shut down if they cannot increase their volume and improve results; however, we need to be very careful defining centers of excellence based on volume alone. Volume determinations are weak and highly variable surrogates for excellent care. In addition to volume, I would add observed to expected mortality, acknowledging the problem with small sample size in these cases, and utilize morbidity and process measurements similar to that provided by The Society of Thoracic Surgeons in conjunction with the National Quality Forum in our nontransplant cases. Finally, we must consider ease of access. Expecting a patient to travel hundreds of miles for a transplant may in the end be worse than going to a low-volume center.

I enjoyed your presentation. I think this will be a very controversial manuscript, and thank you for this opportunity.

**DR WEISS:** Thank you very much, Dr Smedira, for your thoughtful critique and also your kind remarks. I certainly appreciate your comments. Let me answer your questions individually.

In terms of the robustness of the risk assessment, I agree that it would be nice to incorporate mechanical circulatory support as well as diagnoses. Some of these variables are not well represented in the UNOS database, and so we did the best we could with what we had. Ventricular assist device support is unfortunately one of these unrepresented variables. We were able to examine 75 preoperative variables, of which 13 were significant predictors of mortality on univariate analysis. We then incorporated these variables into our multivariable model. Our C-index for that multivariable analysis was 0.68, which is consistent with other reports from the literature, and I think reasonable for a large retrospective multi-institutional database like this. It is not perfect, but I think we did our best given the limitations of our data.

I think that processes of care are very important, as you mentioned. From our analysis, only 2% of the variability in the data is explained by volume. So other processes of care, such as the presence of ancillary staff such as respiratory therapists, specialized providers such as cardiac anesthesiologists, residents and fellows, nurse-to-patient ratio, dedicated intensive care unit intensivists, and many other factors are extremely important. Most of these factors are unfortunately not present in the data set. We would of course have liked to include them. I think only through a multi-institutional study where we can specifically design what variables we want to examine is that achievable.

Your third question was about how to respond to low-volume centers. This is a key point and I thank you for bringing it up. A clear problem is that not all low-volume centers have bad outcomes, and I think it is important to tease out what factors contribute to a center having good or bad outcomes. Clearly, volume is not everything. I think centers that have low volumes should be monitored, and if there is high mortality, then enforceable penalties should exist. However, low-volume centers with low mortality should be allowed to continue to thrive.

I think that identifying additional processes of care will be important for helping low-volume centers that currently do not have good outcomes to improve.

And finally, I will just say that in terms of the difference between 10 and 14, our point was more for proof of concept than anything else. Our intention was to show that a volume cutoff derived from statistical modeling is better than one that is

arbitrarily defined. And so we did our best to use a model to try to define that cutoff of 14. But I wouldn't put tremendous stock into it; as you mentioned, the variability differences are very low. I think it just reinforces the notion that volume is very important in orthotopic heart transplantation and that centers that perform a large volume generally have better outcomes.

Thank you very much again for your thoughtful critique.

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## The Society of Thoracic Surgeons Policy Action Center

The Society of Thoracic Surgeons (STS) is pleased to announce a new member benefit—the STS Policy Action Center, a website that allows STS members to participate in change in Washington, DC. This easy, interactive, hassle-free site allows members to:

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- Research the proposed policies that help—or hurt—one's practice
- Take action on behalf of cardiothoracic surgery

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