How Small Is Too Small? A Systematic Review of Center Volume and Outcome After Cardiac Transplantation

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Background—The aim of this study was to assess the relationship between the volume of cardiac transplantation procedures performed in a center and the outcome after cardiac transplantation.

Methods and Results—PubMed, Embase, and the Cochrane library were searched for articles on the volume–outcome relationship in cardiac transplantation. Ten studies were identified, and all adopted a different approach to data analysis and varied in adjustment for baseline characteristics. The number of patients in each study ranged from 798 to 14,401, and observed 1-year mortality ranged from 12.6% to 34%. There was no association between the continuous variables of center volume and observed mortality. There was a weak association between the continuous variables of center volume and adjusted mortality up to 1 year and a stronger association at 5 years. When centers were grouped in volume categories, low-volume centers had the highest adjusted mortality, intermediate-volume centers had lower adjusted mortality, and high-volume centers had the lowest adjusted mortality but were not significantly better than intermediate-volume centers. Category limits were arbitrary and varied between studies.

Conclusions—There is a relationship between center volume and mortality in heart transplantation. The existence of a minimum acceptable center volume or threshold is unproven. However, a level of 10 to 12 heart transplants per year corresponds to the upper limit of low-volume categories that may have relatively higher mortality. It is not known whether outcomes for patients treated in low-volume transplant centers would be improved by reorganizing centers to ensure volumes in excess of 10 to 12 heart transplants per year. (Circ Cardiovasc Qual Outcomes. 2012;5:783-790.)

Key Words: volume ■ outcome ■ cardiac transplantation ■ mortality
WHAT IS KNOWN

• Registry studies have demonstrated an association between center volume and outcome after cardiac transplantation.
• The number of cardiac transplants performed worldwide is static and low-volume heart transplant centers are common.

WHAT THE STUDY ADDS

• There is a consistent association between center volume and posttransplant mortality across national and international registry studies.
• However, this association is less strong than other important variables such as ischemic time, donor age, or preoperative recipient clinical status.
• The existence of a minimum acceptable center volume is unproven, but analysis by volume category suggests that centers performing under 10 to 12 heart transplants per year may have higher mortality than centers performing >12 transplants per year.

perform 54% of all transplants. Those who call for closure of low-volume transplant centers cite historical registry data that suggest inferior outcomes at low-volume centers. Whether such calls are justified is unclear. Therefore, we conducted a systematic review to define the relationship between center volume and outcome after heart transplantation. We sought to address 2 key issues. Are low-volume centers associated with worse outcome in heart transplantation? Is there a volume threshold below which outcomes are worse?

Methods

The systematic review was performed according to current guidelines. Studies were eligible for inclusion if they described the association between center volume and outcome after heart transplantation. No date or language limitation was imposed. Reports of pediatric cardiac transplantation alone, from single centers or conference abstracts, were excluded. We searched Ovid MEDLINE (1948 to November, week 3, 2011), Embase (1980 to 2011, week 47), and the Cochrane library up to December 3, 2011. The following terms were used to search the databases: heart transplantation, cardiac transplantation, heart transplant, cardiac transplant, volume, center volume, hospital volume, surgeon volume, workload, experience, procedure volume, procedural volume, outcome, treatment outcome, survival, mortality, morbidity, surgical complications, and postoperative complications. In addition, reference lists of all identified publications were manually searched for further studies and websites of organizations responsible for heart transplantation searched.

Two authors (S.P. and P.J.) screened articles by title and abstract. The full text of potentially relevant articles was evaluated. Four studies used data from the Eurotransplant registry. Two studies used Italian and Brazilian national registry data, respectively. The number of centers included in each study ranged from 16 to 265 and number of patients from 798 to 14,401. Six studies included only adult patients, and 4 studies included both pediatric and adult patients. Study populations overlapped between registries and over time; these interrelationships are shown in Figure 2.

Outcome Measures and Analysis

The primary outcome measure in all studies was all-cause mortality among individuals who underwent heart transplantation, measured at intervals from 30 days to 5 years. The most frequent outcome measure was 1-year mortality. One study assessed the composite outcome of all-cause mortality or need for repeat transplantation. Six studies presented unadjusted (observed) mortality, which ranged from 12.6% to 34.1%. All studies also presented mortality adjusted for baseline characteristics, with the exception of a single Italian study. Eight studies defined center volume as the mean number of transplants performed per year during the period of study, and it ranged from 1 year to 7 years. One study defined center volume as the mean number of heart transplants performed per year during the whole transplant program. One study did not define center volume. Six studies examined center volume as a continuous variable. Six studies analyzed center volume by categories. Volume categories were defined using different methods: percentiles (n=2), threshold analysis to define statistically distinct categories (n=1), or by unspecified methods (n=3). Two studies provided limited data about surgeon volume; observed mortality did not differ with previous surgical experience.

Assessment of Bias

Overlap between study data sets is a major source of bias (Figure 2). Three UNOS registry studies overlapped in time. One ISHLT registry study shared data with 3 UNOS
Figure 1. Study selection.

Table 1. Characteristics of the 10 Studies That Have Assessed the Relationship Between Center Volume and Clinical Outcome After Cardiac Transplantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>Year</th>
<th>Centers</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Continuous Data</th>
<th>Categorical Data</th>
<th>Additional Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laffel et al15</td>
<td>US, ISHLT</td>
<td>1984–1986</td>
<td>56</td>
<td>1123</td>
<td>90-d mortality</td>
<td>Yes</td>
<td>No</td>
<td>First 10 cases per unit excluded to avoid learning curve</td>
</tr>
<tr>
<td>Evans et al16</td>
<td>ISHLT</td>
<td>1988</td>
<td>106</td>
<td>1602</td>
<td>1-y survival</td>
<td>No</td>
<td>Yes</td>
<td>Multivariable analysis using a piecewise exponential hazards modeling approach</td>
</tr>
<tr>
<td>Stehlik et al24</td>
<td>ISHLT</td>
<td>2000–2009</td>
<td>265</td>
<td>10 271,*</td>
<td>1-y mortality, 5-y mortality</td>
<td>No</td>
<td>Yes</td>
<td>Multivariable analysis using proportional hazards model. Continuous factors were fit using a restricted cubic spline.</td>
</tr>
<tr>
<td>Hosenpud et al17</td>
<td>US, UNOS</td>
<td>1987–1991</td>
<td>150</td>
<td>7893</td>
<td>1-mo mortality, 1-y mortality</td>
<td>Yes</td>
<td>Yes</td>
<td>Mortality data adjusted for baseline characteristics using generalized additive model and 4 covariables</td>
</tr>
<tr>
<td>Shuhalber et al18</td>
<td>US, UNOS</td>
<td>1999–2005</td>
<td>147</td>
<td>13 230</td>
<td>1-y mortality</td>
<td>No</td>
<td>Yes</td>
<td>Multivariable analysis using Cox proportional hazards modeling</td>
</tr>
<tr>
<td>Weiss et al19</td>
<td>US, UNOS</td>
<td>1999–2006</td>
<td>143</td>
<td>14 401</td>
<td>30-d mortality, 1-y mortality‡</td>
<td>Yes</td>
<td>Yes</td>
<td>Multivariable analysis using Cox proportional hazards regression model with factors found to be significant on univariable analysis</td>
</tr>
<tr>
<td>Russo et al20</td>
<td>US, UNOS</td>
<td>2001–2006</td>
<td>143</td>
<td>8029</td>
<td>1-y mortality or repeat transplantation</td>
<td>No</td>
<td>Yes</td>
<td>Multivariable logistic regression analysis</td>
</tr>
<tr>
<td>Bocchi et al22</td>
<td>Brazil</td>
<td>1984–1999</td>
<td>16</td>
<td>798</td>
<td>1-y mortality</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Smits et al21</td>
<td>Europe, ET</td>
<td>1997–1998</td>
<td>45</td>
<td>1401</td>
<td>1-y survival</td>
<td>Yes</td>
<td>No</td>
<td>Multivariable modeling of expected mortality rates by Cox proportional hazards regression analysis, followed by 2 models of case-mix adjusted center volume effect</td>
</tr>
<tr>
<td>Taioli et al23</td>
<td>Italy</td>
<td>2000–2002</td>
<td>16</td>
<td>843 adult§</td>
<td>1-y organ survival</td>
<td>Yes</td>
<td>No</td>
<td>Multivariable modeling of expected mortality rates by Cox proportional hazards regression analysis</td>
</tr>
</tbody>
</table>

ISHLT indicates International Society for Heart and Lung Transplantation; UNOS, United Network for Organ Sharing; ET, Eurotransplant.

Details of the additional analysis are listed in Appendix in the online-only Data Supplement.

*Patients included in 1-y analysis.
†Patients included in 5-y analysis.
‡Five-year mortality conditional on survival at 1 year.
§Age unspecified.
and 1 Italian national registry studies.\textsuperscript{1,18–20,22} Another ISHLT registry study shared data with 1 UNOS and 1 Brazilian national registry study.\textsuperscript{16,17,22} As such, an unknown number of patients contributed data to multiple studies, introducing bias that is difficult to quantify or control. Selection and reporting bias within registries should be minimized by the mandatory requirement to register and report outcomes for every consecutive heart transplant, although it remains possible that loss to follow-up could create bias. Missing data were unusual in the UNOS registry, which had 90% to 99% data entry for the majority of variables.\textsuperscript{20} Finally, high-volume centers tended to perform heart transplants in patients with a higher preoperative risk profile. Each multivariable analysis used different baseline characteristics and this may introduce performance bias if there was variation in adjustment for preoperative risk profile between centers (see Appendix in the online-only Data Supplement).

**Center Volume as a Continuous Variable (Unadjusted)**

Four studies, using data from ISHLT, UNOS, and Eurotransplant, examined the relationship between center volume as a continuous variable and observed mortality (Table 1).\textsuperscript{15,17,19,22} None identified a linear association between center volume and observed mortality. Only 1 study provided a statistical test; the Pearson correlation coefficient was \( -0.03 \).\textsuperscript{15} All 4 studies plotted center volume against observed mortality; charts from the most recent UNOS and Eurotransplant studies are reproduced in Figure 3. As would be expected as a result of sampling variability and the play of chance, there was greater mortality variation in lower-volume centers.

**Center Volume as a Continuous Variable (Adjusted)**

Four studies examined the relationship between center volume as a continuous variable and mortality adjusted for baseline characteristics.\textsuperscript{1,19,21,23} In a report from Italy, a Cox proportional hazards model was used to generate adjusted risk of death for each center and there was no correlation with center volume (Pearson correlation coefficient, \( -0.38; P=0.17 \)).\textsuperscript{23} A similar study of Eurotransplant data generated expected mortality rates for each center using a Cox proportional hazards model.\textsuperscript{21} There was a weak association between center volume and adjusted hazard of death (regression coefficient, \( -0.0082; P=0.02 \)). In a multivariable analysis of UNOS data, lower center volume was associated with increased 30-day mortality; for every 1 case fewer per year from the median center volume, the odds of death at 30 days increased (odds ratio, 1.02; 95% confidence interval [CI], 1.01–1.03; \( P<0.001 \)).\textsuperscript{19} The most recent analysis of the ISHLT registry is shown in Figure 4; there was a significant relationship between center volume, modeled as a restricted cubic spline, and mortality at 1 year (\( P=0.0378 \)) and a stronger relationship at 5 years (\( P<0.0001 \)).\textsuperscript{1,24}

**Center Volume as a Categorical Variable (Unadjusted)**

Four studies examined the relationship between center volume as a categorical variable and observed mortality. Data from the ISHLT registry in 1988 showed no significant difference in observed mortality by center volume category.\textsuperscript{16} A study of 16 Brazilian transplant centers reported no significant difference in observed mortality by center volume category.\textsuperscript{22} Two larger US studies using the UNOS registry demonstrated lower observed mortality in high-volume centers.\textsuperscript{17,19} In the most recent of these studies (covering the period 1999 to 2006), observed 1-year mortality was 16.2% in centers performing <10 transplants per year compared with 12.2% in centers performing \( \geq 10 \) transplants per year. This survival difference remained significant at 5 years by Kaplan-Meier analysis (log rank, \( P<0.001 \)).\textsuperscript{19}

**Center Volume as a Categorical Variable (Adjusted)**

One study using ISHLT data from 1988 examined the relationship between center volume as a categorical variable and mortality in a multivariable analysis.\textsuperscript{16} However, the volume categories did not include all centers, statistical methods were not described, and no CIs were presented.\textsuperscript{16} Four further studies, all from the UNOS registry and with overlapping time periods, examined the relationship between center volume as a categorical variable and mortality adjusted for baseline characteristics (Table 2).\textsuperscript{17–20} Direct comparison between studies is hindered by heterogeneous statistical adjustment for baseline characteristics. However, several observations can be made. Every study demonstrated an association between higher center volume and lower mortality. Mortality was significantly higher in the lowest volume centers compared with intermediate- and high-volume centers. However, differences in mortality between intermediate- and high-volume centers were not significant.

**Is There a Threshold in the Volume–Outcome Relationship?**

Only 1 study has examined multiple center volume thresholds in a single data set.\textsuperscript{15} In a multivariable logistic regression analysis of 30-day mortality, an excess risk of death was seen at center...
volumes of <10 transplants per year (hazard ratio, 2.02; 95% CI, 1.46–2.80), <5 transplants per year (hazard ratio, 1.86; 95% CI, 1.04–3.32), and ≤2 transplants per year (hazard ratio, 2.15; 95% CI, 1.02–4.56). Sequential multivariable logistic regression at all center volumes was conducted. Center volume was a poor predictor of 30-day mortality at all volume thresholds, with an area under the receiver operating curve of 0.64 to 0.665. No threshold of center volume reliably predicted mortality with greater accuracy. No data exist to support a threshold in what appears to be a continuous relationship between volume and outcome. Any thresholds suggested by categorical volume analysis are arbitrary.

**Discussion**

We identified 10 studies that describe the association between center volume and clinical outcome after cardiac transplantation in adults. There was no association between the continuous variable of center volume and crude mortality. There was a weak association between the continuous variable of center volume and adjusted mortality at 30 days and 1 year, but a clearer association with mortality was seen at 5 years. When centers were grouped in volume categories, there was a clear and consistent association between center volume and mortality. Low-volume centers had the worst outcomes. Intermediate-volume centers had better outcomes than low-volume centers. High-volume centers had the best outcomes but were not significantly better than intermediate volume centers.

**Statistical Limitations**

Sampling variation is a major problem when assessing outcomes after heart transplantation, both during routine center surveillance and in studies of center volume–outcome relationship. It is inevitable that low-volume centers will exhibit greater variation in mortality than high-volume centers within a fixed time period, simply because of the play of chance. It is
challenging to separate true between-center differences from random sampling variation. The association between mortality and volume as a continuous variable may be concealed by high variation in mortality in low-volume centers. This variation is clearly seen in scatterplots of center volume versus observed mortality (Figure 3). These scatterplots also suggest a threshold effect, rather than a linear or exponential association, arguably justifying analysis by volume category. Finally, statistical techniques such as multivariable analysis may overstate the importance of variables such as center volume. In the most recent ISHLT analysis, center volume was estimated to account for <1% of total mortality variance after cardiac transplantation.

The evidence has many limitations, the foremost being reliance on UNOS registry reports that overlap in time. Only 3 studies contained solely non-US data. Little is known about the volume–outcome relationship in much of Europe, Asia, or Australia. Population density, donor organ availability, and transport systems are important for transplantation and may influence the volume–outcome relationship. A further limitation is that all studies had mortality as the sole outcome measure and only 2 studies assessed outcomes beyond 1 year. No studies addressed pretransplant outcomes (waiting list mortality) or long-term posttransplant outcomes such as quality of life, graft rejection, or vasculopathy and need for further interventions such as renal replacement therapy or repeat transplantation. Finally, much of the published registry data are old. Five studies used 20th century data, before advances in antibody detection, immunosuppression, and short-term mechanical circulatory support after transplantation. However, it is noteworthy that the volume–outcome relationship appears to be relatively consistent in studies spanning 3 decades of transplantation.

Can Low-Volume Transplant Centers Have Satisfactory Outcomes?

Two studies described the performance of individual, small centers. Using an empirical Bayes estimate of center effects, 18 of 20 centers in the Eurotransplant registry with an annual

<table>
<thead>
<tr>
<th>Study</th>
<th>Measurement</th>
<th>Outcome Measure</th>
<th>Volume Category 1</th>
<th>Volume Category 2</th>
<th>Volume Category 3</th>
<th>Volume Category 4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosenpud et al17</td>
<td>Probability of death for typical patient*</td>
<td>1-y mortality</td>
<td>&lt;9 CTX/y</td>
<td>&gt;9 CTX/y</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shuheiber et al20</td>
<td>Multivariable analysis hazard ratio (95% CI)</td>
<td>1-y mortality</td>
<td>reference</td>
<td>0.71 (0.62-0.82)</td>
<td>0.64 (0.56-0.74)</td>
<td>0.56 (0.48–0.65)</td>
<td></td>
</tr>
<tr>
<td>Weiss et al18</td>
<td>Multivariable analysis odds ratio (95% CI)</td>
<td>30d mortality</td>
<td>≤2 CTX/y</td>
<td>&gt;2 CTX/y</td>
<td>reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russo et al19</td>
<td>Stratum-specific likelihood ratio (95% CI)</td>
<td>1-y mortality or repeat transplantation</td>
<td>reference</td>
<td>0.35 (0.22-0.56)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Clinical Outcomes With Adjustment for Baseline Characteristics Subdivided by Volume Category**

CTX indicates cardiac transplant; CI, confidence interval.

*Typical patient defined as hospitalized patient with noncongenital heart disease undergoing first transplantation performed at the midpoint of the study duration.
volume of <10 transplants per year had mortality rates in keeping with their case mix.21 In contrast, only 2 of 4 centers in the Italian national registry with an annual volume of <10 transplants per year had mortality rates in keeping with their case mix.22 Low-volume transplant centers may have satisfactory outcomes but require surveillance. Because low-volume centers are expected to have a large variation in annual mortality rates, simply through sampling variation, statistical process control techniques such as cumulative sum charts are required to monitor performance.23,24 There are no international guidelines regarding acceptable volumes for heart transplant centers. In the United States, Centers for Medicare and Medicaid Services require heart transplant centers to perform at least 10 transplants per year and centers are defined as functionally inactive if no transplants are performed for 3 months.25

Should Transplant Centers Be Reorganized to Ensure That All Have Acceptable Annual Volume? It has been argued that outcomes could be improved if low-volume centers were closed and patients traveled to high-volume centers.8,9 Higher-volume centers may achieve absolute risks for unadjusted mortality of up to 4% lower.19 Smaller reductions in absolute risk have justified the reorganization of reperfusion therapy in acute ST-segment elevation myocardial infarction. In the only study to address the issue, patient home-to-transplant center distances of >300 miles did not reduce survival or increase complications after cardiac transplantation in the United States.26 These arguments may be flawed. First, the incremental mortality reduction associated with transplantation in a higher-volume center may not be clinically meaningful. For example, closure of a low-volume center with a mortality rate of 16% would save 1 life every 2.5 years if all patients were transplanted at a high-volume center with a mortality rate of 12%.19 Second, closure of low-volume transplant centers has never been demonstrated to improve outcomes. There may be unexpected adverse effects, such as reduced rates of referral for transplantation, increased waiting list mortality, a reduced pool of organs available for transplantation, or prolonged ischemic times resulting in worse outcomes for patients with advanced heart failure.

Conclusions There is undoubtedly a relationship between the volume of heart transplants performed and mortality. The existence of an optimal or minimum acceptable center volume is uncertain. However, an annual volume of 10 to 12 transplants corresponds with the upper limit of low-volume categories that may have relatively higher mortality. It is unclear whether outcomes for patients treated in low-volume transplant centers would be improved by reorganizing centers to ensure volumes in excess of 10 to 12 heart transplants per year. Closing transplant centers may have adverse consequences on other factors, such as ischemic time, that are associated with worse outcome. These issues should be explored before transplant services are reorganized.

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References


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Appendix


Shuheiber 2010. Donor variables analyzed include age, gender, and cold ischemia time. Recipient variables analyzed include age, gender, race, body mass index, diagnoses (including primary reason for transplantation, presence of hypertension, diabetes, need for renal replacement therapy, or mechanical ventilation), creatinine, bilirubin, cardiac output, and presence or absence of a left ventricular assist device.

Weiss 2008. Variables in multivariable analysis for mortality: 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 anastamotic technique, need for mechanical ventilation before undergoing transplantation, and transplantation year.

Russo 2010. Variables in multivariate analysis for one year mortality or retransplantation: recipient age (40 years, 40 to 54 years, 55 to 69 years, 70 years); recipient heart failure aetiology (congenital, hypertrophic, ischemic, restrictive, sarcoidosis, valvular, other); recipient previous heart transplant within 90 days; recipient pulmonary vascular resistance (PVR) >4 Wood units; recipient estimated glomerular filtration rate (<33 mL/min, 33-53 mL/min, >53 mL/min); recipient total bilirubin >2.0 mg/dL; recipient diabetes mellitus; recipient peripheral vascular disease; recipient receiving steroids at transplant; recipient need for ventilator; recipient hypertension; recipient extracorporeal membrane oxygenation (ECMO) at transplant; recipient extracorporeal left ventricular assist device—only at transplant; recipient intracorporeal left ventricular assist device—only at transplant; recipient right ventricular assist device—only at transplant; recipient biventricular assist device at transplant; recipient paracorporeal ventricular assist device at transplant; recipient total artificial
heart at transplant; recipient intraaortic balloon pump at transplant; recipient in intensive care unit at transplant; recipient hospitalized at transplant; donor age (20-29 years, 30-39 years, 40-50 years and >50 years); donor:recipient weight ratio of 0.8; female donor to male recipient; female donor to female recipient; female donor to male recipient; male donor to female recipient; kidney donor concurrently; lung donor concurrently; pancreas donor concurrently; ischemic time (<1 hour, 1-4 hours, and >4 hours); mean number of heart transplants per center per year; and year of transplant.

Smits 2003. Variables in the Cox proportional hazards model: recipient gender, recipient age, disease, mechanical support at time of offer, respirator, inotropic support, serum creatinine (mg/dL), cold ischemic time, donor age, donor gender, cause of death (donor), local donor, residence at time of offer, donor:recipient weight match.

Taioli 2005. Variables in the Cox proportional hazards model: ischemia time, recipient age, recipient gender, donor age, number of previous transplants, previous pathology, combined transplant, vascular resistance, creatinine, bilirubin, type of transplant, previous cardiac surgery, weight match, hospitalization prior to transplant, coronary angiography, echocardiography.