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

Stephen J. Pettit, MBBS, PhD; Pardeep S. Jhund, MBChB, MSc, PhD;
Nathaniel M. Hawkins, MBChB, MD, MPH; Roy S. Gardner, MBChB, MD;
Saleem Haj-Yahia, MD; John J.V. McMurray, MBChB, MD; Mark C. Petrie, MBChB

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

Heart transplantation remains an important therapy for patients with end-stage heart failure. Approximately, 5800 transplants are performed worldwide each year.[1] The International Society for Heart and Lung Transplantation (ISHLT) registry collects data from 388 heart transplant centers from the United States, Europe, Australia, and New Zealand (covering approximately 66% of heart transplants performed worldwide) and has reported that the number of heart transplants has decreased by 25% since the mid-1990s.[1] A similar trend is seen in the Eurotransplant area, comprising Austria, Belgium, Croatia, Germany, Slovenia, and the Netherlands, where average annual volume has fallen from 752 heart transplants between 1991 and 1995 to 573 heart transplants between 2006 and 2010.[2] In the United Kingdom, average annual volume has fallen from 196 heart transplants between 1996 and 2002 to a nadir of 86 heart transplants in 2009 and 2010.[3]

There is a concern that centers may not be performing a sufficient number of heart transplants to maintain adequate skill and experience in the procedure. The relationship between center volume and outcome after surgical procedures is well established.[4] Compared with low-volume centers, high-volume centers report lower mortality for coronary artery bypass grafting,[5] surgery for pediatric congenital heart disease,[6] and renal and liver transplantation.[7] Concerns that the same principle applies to cardiac transplantation have led to pressure to reorganize cardiac transplantation services around regional or national centers.[8–10] The effect of reorganization is uncertain, but the availability of heart transplantation could decrease if referral rates or donor organ use fall as a result of more distant transplant centers.

Within the ISHLT registry, low-volume centers performing <10 transplants per year account for 40% of centers, but only perform 13% of all transplants. Centers that perform 10 to 19 transplants per year account for 39% of centers and perform 33% of transplants. High-volume centers performing >20 transplants per year account for only 21% of centers, but

perform 54% of all transplants.[1] 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.[11] 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. Articles were included if the subject was cardiac transplantation, if center volume was an independent variable, and if the outcome or the association between volume and outcome was described. Discrepancies regarding inclusion or exclusion of articles were resolved by discussion. One author (S.P.) extracted and tabulated data from all included articles. Two authors (P.J. and N.H.) checked the accuracy of extracted data. The following data were extracted: source of data, number of patients, number of centers, center volume (described as a continuous or categorical variable), limits of volume categories, outcomes and additional analyses performed to adjust for case mix. Outcome data unadjusted for case mix were summarized as percent mortality

at specified time points after cardiac transplantation. Outcome data adjusted for case mix were summarized using different measures in each study, including odds ratios, hazard ratios, stratum-specific likelihood ratios, and observed-to-expected mortality ratios. Study results were not combined on the basis of statistical and clinical judgment.[12,13] A combination of different outcome measures reported and different methods of adjustment in multivariable models meant that meta-analysis was likely to be biased even if alternative methods of meta-analysis were used.[14] Forest plots were not produced for this reason and data are summarized in tables.

Results

Study Selection

Of 2715 articles screened, 10 studies assessed the relationship between center volume and clinical outcome after cardiac transplantation (Figure 1). The characteristics of each study are described in Table 1.[1,15–24] One study conducted in the United States before 1987 used data from US centers in the ISHLT registry, combined with data obtained directly from transplant centers.[15] Two studies used data from the ISHLT registry.[1,16] Four studies used data from the United Network for Organ Sharing (UNOS) registry.[17–20] One study used data from the Eurotransplant registry.[21] Two studies used Italian and Brazilian national registry data, respectively.[22,23] 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,[1,18–21,23] and 4 studies included both pediatric and adult patients.[15–17,22] 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.[20] Six studies presented unadjusted (observed) mortality,[16–19,22,23] which ranged from 12.6%[19] to 34.1%.[22] All studies also presented mortality adjusted for baseline characteristics, with the exception of a single Italian study.[22] 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.[15–21,23] One study defined center volume as the mean number of heart transplants performed per year during the whole transplant program.[22] One study did not define center volume.[1] Six studies examined center volume as a continuous variable.[1,15,17,19,21,23] Six studies analyzed center volume by categories.[16–20,22] Volume categories were defined using different methods: percentiles (n=2),[18,22] threshold analysis to define statistically distinct categories (n=1),[20] or by unspecified methods (n=3).[16,17,19] Two studies provided limited data about surgeon volume; observed mortality did not differ with previous surgical experience.[15,16]

Assessment of Bias

Overlap between study data sets is a major source of bias (Figure 2). Three UNOS registry studies overlapped in time.[18–20] One ISHLT registry study shared data with 3 UNOS
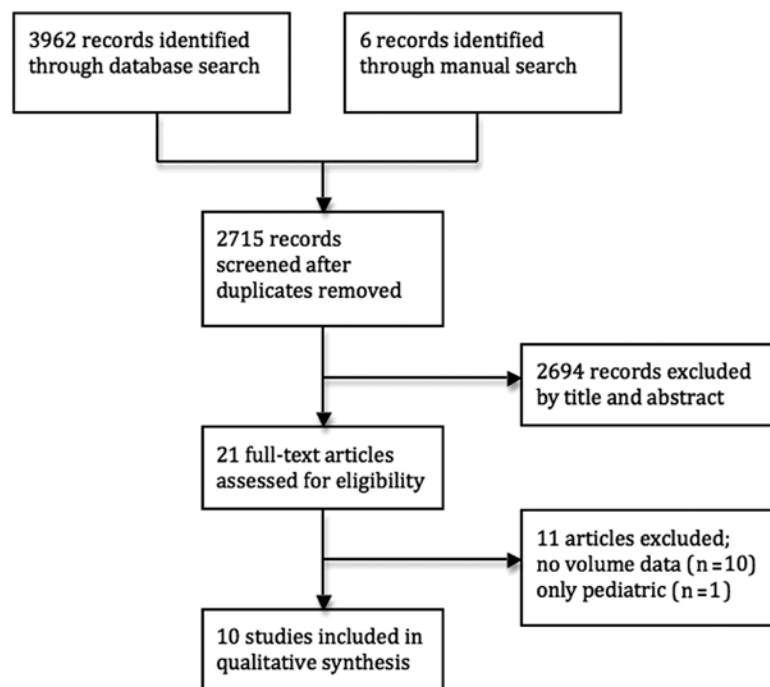
Figure 1. Study selection.

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

Study	Source	Year	Centers	Patients	Outcomes	Continuous Data	Categorical Data	Additional Analysis
Laffel et al[15]	US, ISHLT	1984–1986	56	1123 all ages	90-d mortality	Yes	No	First 10 cases per unit excluded to avoid learning curve
Evans et al[16]	ISHLT	1988	106	1602 all ages	1-y survival	No	Yes	Multivariable analysis using a piecewise exponential hazards modeling approach
Stehlik et al[1,24]	ISHLT	2000–2009	265	10 271,* 10 785,† >18 y	1-y mortality, 5-y mortality	Yes	No	Multivariable analysis using proportional hazards model. Continuous factors were fit using a restricted cubic spline.
Hosenpud et al[17]	US, UNOS	1987–1991	150	7893 all ages	1-mo mortality, 1-y mortality	Yes	Yes	Mortality data adjusted for baseline characteristics using generalized additive model and 4 covariables
Shuhaiber et al[18]	US, UNOS	1999–2005	147	13 230 >18 y	1-y mortality	No	Yes	Multivariable analysis using Cox proportional hazards modeling
Weiss et al[19]	US, UNOS	1999–2006	143	14 401 >18 y	30-d mortality, 1-y mortality, 5-y mortality‡	Yes	Yes	Multivariable analysis using Cox proportional hazards regression model with factors found to be significant on univariable analysis
Russo et al[20]	US, UNOS	2001–2006	143	8029 >18 y	1-y mortality or repeat transplantation	No	Yes	Multivariable logistic regression analysis
Bocchi et al[22]	Brazil	1984–1999	16	798 all ages	1-y mortality	No	Yes	None
Smits et al[21]	Europe, ET	1997–1998	45	1401 >16 y	1-y survival	Yes	No	Multivariable modeling of expected mortality rates by Cox proportional hazards regression analysis, followed by 2 models of case-mix adjusted center volume effect
Taioli et al[23]	Italy	2000–2002	16	843 adult§	1-y organ survival	Yes	No	Multivariable modeling of expected mortality rates by Cox proportional hazards regression analysis

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.
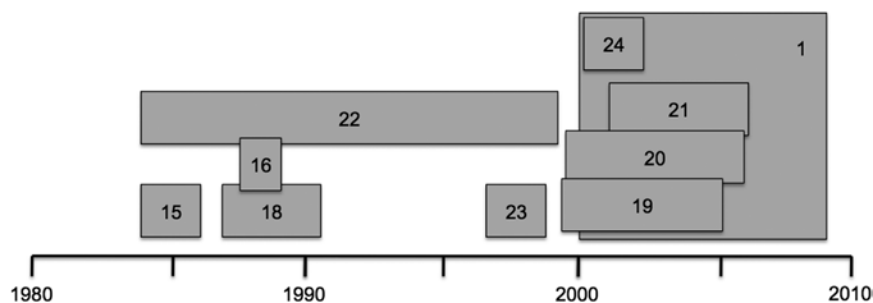
§Age unspecified.

Figure 2. Study interrelationship. Interrelationship among 10 studies included. Partially or completely overlapping boxes indicate, respectively, a partial or complete overlap in the registry from which the study population was obtained. Each study is numbered as referenced.

and 1 Italian national registry studies.[1,18–20,23] Another ISHLT registry study shared data with 1 UNOS and 1 Brazilian national registry study.[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.[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).[15,17,19,21] 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.[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.[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).[23] A similar study of Eurotransplant data generated expected mortality rates for each center using a Cox proportional hazards model.[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).[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).[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.[16] A study of 16 Brazilian transplant centers reported no significant difference in observed mortality by center volume category.[22] Two larger US studies using the UNOS registry demonstrated lower observed mortality in high-volume centers.[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 ≥10 transplants per year. This survival difference remained significant at 5 years by Kaplan-Meier analysis (log rank, *P*<0.001).[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.[16] However, the volume categories did not include all centers, statistical methods were not described, and no CIs were presented.[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).[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.[19] In a multivariable logistic regression analysis of 30-day mortality, an excess risk of death was seen at center
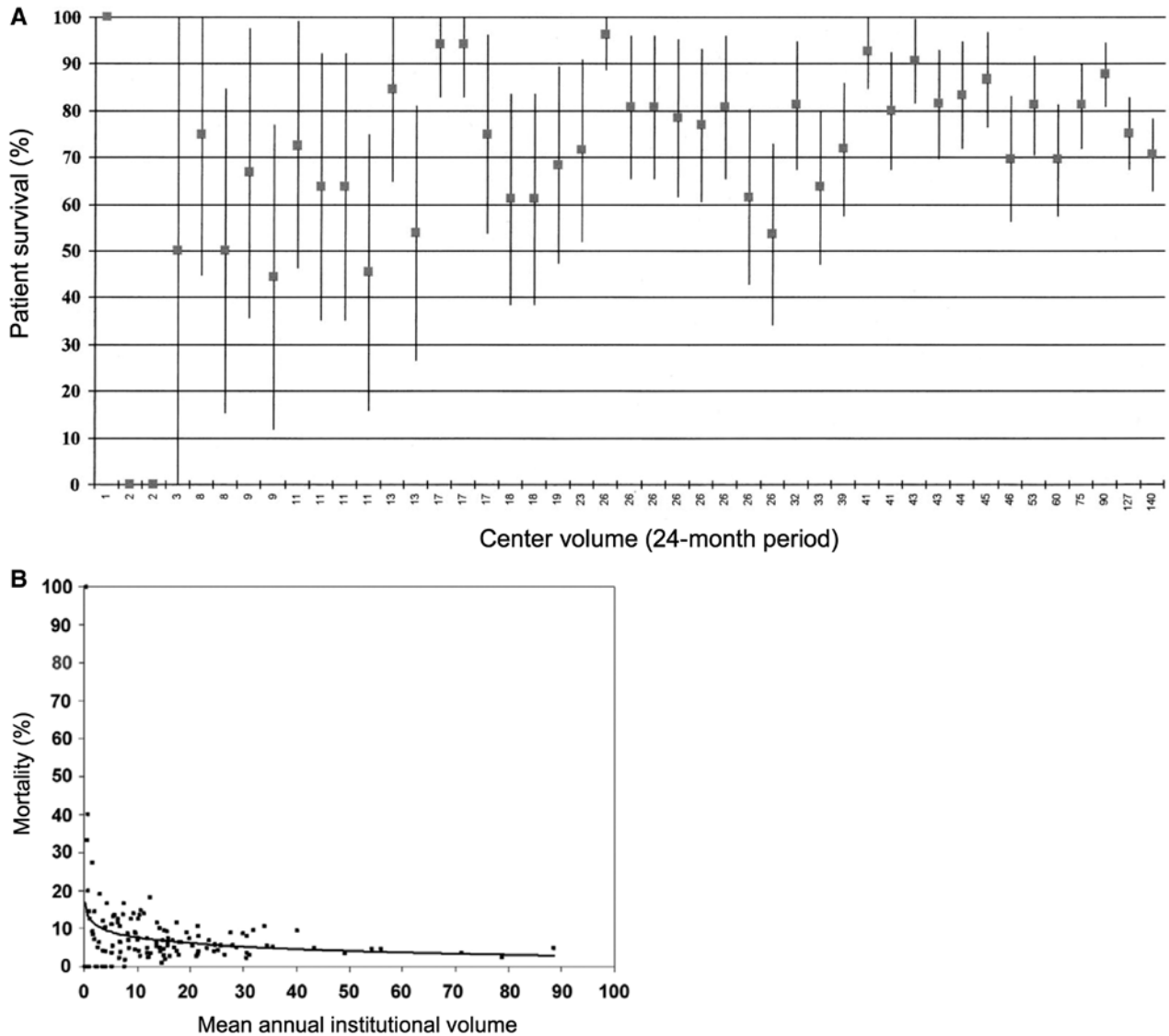
Figure 3. Center volume vs crude mortality. **A**, Patient survival at 1 year posttransplant (with 95% confidence intervals), ordered by center volume over the 2-year study period in the Eurotransplant registry.[21] **B**, Patient mortality at 30 days posttransplant vs center volume in the United Network for Organ Sharing registry.[19] Reproduced with permission of Wolters Kluwer Health and Elsevier Inc, respectively.

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.[19] 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
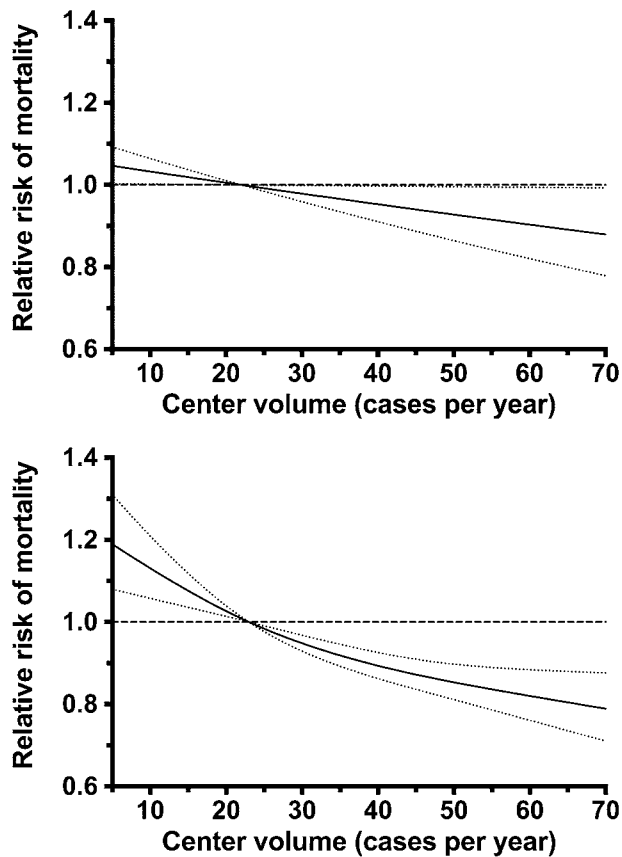
Figure 4. Center volume vs adjusted mortality in the International Society for Heart and Lung Transplantation registry. Relative risk of mortality by center volume at 1 year (**Upper**) and 5 years (**Lower**) after heart transplantation in the 2011 report from the International Society for Heart and Lung Transplantation registry.[1] The dotted lines represent upper and lower 95% confidence intervals. One-year mortality is compared with the median center volume of 22 cases per year. Five-year mortality is compared with the median center volume of 23 cases per year.

challenging to separate true between-center differences from random sampling variation.[21] 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, the relationship between center volume and mortality was less strong than for every other significant risk factor for mortality at 1 year and the majority of risk factors at 5 years.[1,24] In the most detailed UNOS analysis, center volume was estimated to account for <1% of total mortality variance after cardiac transplantation.[19]

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.[21–23] 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.[1,19] 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.[15–17,21,22] 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 2.   Clinical Outcomes With Adjustment for Baseline Characteristics Subdivided by Volume Category

Study	Measurement	Outcome Measure	Volume Category 1 (Lowest)	Volume Category 2	Volume Category 3	Volume Category 4 (Highest)	P
Hosenpud et al[17]	Probability of death for typical patient*	1-y mortality	<9 CTX/y 21%	>9 CTX/y 17%			<0.001
Shuheiber et al[20]	Multivariable analysis hazard ratio (95% CI)	1-y mortality	0-11 CTX/y reference	12-21 CTX/y 0.71 (0.62-0.82)	22–33 CTX/y 0.64 (0.56–0.74)	≥34 CTX/y 0.56 (0.48–0.65)	
Weiss et al[18]	Multivariable analysis odds ratio (95% CI)	30d mortality	≤2 CTX/y 2.15 (1.02-4.56) <5 CTX/y 1.86 (1.04-3.32) <10 CTX/y 2.02 (1.46-2.80) <40 CTX/y reference	>2 CTX/y reference >5 CTX/y reference >10 CTX/y reference ≥40 CTX/y 0.35 (0.22-0.56)			
Russo et al[19]	Stratum-specific likelihood ratio (95% CI)	1-y mortality or repeat transplantation	<10.5 CTX/y 1.37 (1.23-1.53)	10.5-47 CTX/y 0.96 (0.91-1.0)	>47 CTX/y 0.84 (0.74–0.95)		

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.[23] 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.[25,26] 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.[27]

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.[28] 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.

Acknowledgments

Sources of Funding

Disclosures

References

1. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, Kirk R, Rahmel AO, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth adult heart transplant report—2011. *J Heart Lung Transplant*. 2011;30:1078–1094.
2. Oosterlee A, Rahmel A. *Eurotransplant International Foundation annual report 2010*. Leiden, Holland: Eurotransplant; 2011.
3. Rogers C, Emin A, Thomas H, Van der Meulen J, Parameshwar J, Bonser RS, Banner NR. UK Cardiothoracic Transplant Audit. The Royal College of Surgeons of England and NHS Blood and Transplant; http://www.rcseng.ac.uk/surgeons/research/surgical-research/docs/uk-cardiothoracic-transplant-audit-report-2011/view. Accessed October 29, 2012.
4. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. *N Engl J Med*. 1979;301:1364–1369.
5. Wu C, Hannan EL, Ryan TJ, Bennett E, Culliford AT, Gold JP, Isom OW, Jones RH, McNeil B, Rose EA, Subramanian VA. Is the impact of hospital and surgeon volumes on the in-hospital mortality rate for coronary artery bypass graft surgery limited to patients at high risk? *Circulation*. 2004;110:784–789.
6. Spiegelhalter DJ. Mortality and volume of cases in paediatric cardiac surgery: retrospective study based on routinely collected data. *BMJ*. 2002;324:261–263.
7. Axelrod DA, Guidinger MK, McCullough KP, Leichtman AB, Punch JD, Merion RM. Association of center volume with outcome after liver and kidney transplantation. *Am J Transplant*. 2004;4:920–927.
8. Dellgren G, Sigurdardottir V, Berg CH, Rundqvist B, Haraldsson A, Berggren H, Lidén H, Kjellman U, Karason K, Wiklund L, Andersson B, Nilsson F, Berglin E. [Better and better results of heart transplantation. Analysis of 25 years of collected experiences]. *Lakartidningen*. 2009;106:3332–3337.
9. Hultman J, Tibell A, Linde C. [What determines successful heart transplantation care? Low volume alone does not explain the decrease in 1-year survival]. *Lakartidningen*. 2010;107:368, 370.
10. Macgowan GA, Parry G, Schueler S, Hasan A. The decline in heart transplantation in the UK. *BMJ*. 2011;342:d2483.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
12. Higgins JPT, Green S, eds. Analysing data and undertaking meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011*. www.cochrane-handbook.org. Accessed July 25 2012.
13. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ*. 1998;316:140–144.
14. Ioannidis JP, Patsopoulos NA, Rothstein HR. Reasons or excuses for avoiding meta-analysis in forest plots. *BMJ*. 2008;336:1413–1415.
15. Laffel GL, Barnett AI, Finkelstein S, Kaye MP. The relation between experience and outcome in heart transplantation. *N Engl J Med*. 1992;327:1220–1225.
16. Evans RW, Dong FB, Manninen DL. The center effect in heart transplantation. In: Terasaki P, ed. *Clinical Transplants*. Los Angeles, CA: UCLA Tissue Typing Laboratory; 1992;45–59.
17. Hosenpud JD, Breen TJ, Edwards EB, Daily OP, Hunsicker LG. The effect of transplant center volume on cardiac transplant outcome: a report of the United Network for Organ Sharing Scientific Registry. *JAMA*. 1994;271:1844–1849.
18. Shuhaiber JH, Moore J, Dyke DB. The effect of transplant center volume on survival after heart transplantation: a multicenter study. *J Thorac Cardiovasc Surg*. 2010;139:1064–1069.
19. Weiss ES, Meguid RA, Patel ND, Russell SD, Shah AS, Baumgartner WA, Conte JV. Increased mortality at low-volume orthotopic heart transplantation centers: should current standards change? *Ann Thorac Surg*. 2008;86:1250–1259.
20. Russo MJ, Iribarne A, Easterwood R, Ibrahimiye AN, Davies R, Hong KN, Ascheim DD, Gelijns AC, Naka Y. Post-heart transplant

survival is inferior at low-volume centers across all risk strata. *Circulation*. 2010;122:S85–S91.

21. Smits JM, De Meester J, Deng MC, Scheld HH, Hummel M, Schoendube F, Haverich A, Vanhaecke J, van Houwelingen HC, COCPIT Study Group, Eurotransplant heart transplant programs. Mortality rates after heart transplantation: how to compare center-specific outcome data? *Transplantation*. 2003;75:90–96.

22. Bocchi EA, Fiorelli A, First Guideline Group for Heart Transplantation of the Brazilian Society of Cardiology. The Brazilian experience with heart transplantation: a multicenter report. *J Heart Lung Transplant*. 2001;20:637–645.

23. Taioli E, Venettoni S, Pretagostini R, Roggero S, Scalamogna M, Mattucci DA, Costa AN. Quality evaluation of solid organ transplant in Italy for the period 2000 to 2002 data from the National Transplant Center. *Transplant Proc*. 2005;37:4163–4169.

24. Overall Heart and Adult Heart Transplantation Statistics 2011. www.ishlt.org/downloadables/slides/2011/heart_adult.ppt. Accessed February 17, 2012.

25. Axelrod DA, Kalbfleisch JD, Sun RJ, Guidinger MK, Biswas P, Levine GN, Arrington CJ, Merion RM. Innovations in the assessment of transplant center performance: implications for quality improvement. *Am J Transplant*. 2009;9:959–969.

26. Rogers CA, Ganesh JS, Banner NR, Bonser RS, Steering Group. Cumulative risk adjusted monitoring of 30-day mortality after cardiothoracic transplantation: UK experience. *Eur J Cardiothorac Surg*. 2005;27:1022–1029.

27. The Center for Medicare and Medicaid Services. Medicare program; Hospital conditions of participation: requirements for approval and reapproval of transplant centers to perform organ transplants. *Fed Regist*. 2007;15197–15280.

28. Rodkey SM, Hobbs RE, Goormastic M, Young JB. Does distance between home and transplantation center adversely affect patient outcomes after heart transplantation? *J Heart Lung Transplant*. 1997;16:496–503.

Appendix

Hosenpud 1994. Covariates in analysis: first versus repeat transplantation, medical condition at time of transplantation (home, hospital, ITU), congenital heart disease, date of transplantation.

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.