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Extracorporeal membrane oxygenation as a bridge to lung transplantation: what lessons might we learn from volume and expertise?

Jeremiah W. Awori Hayanga[a,*], Alena Lira[b], Jonathan K. Aboagye[c], Heather K. Hayanga[d] and Jonathan D'Cunha[a]

[a] Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[b] Department of Surgical Critical Care, MedStar Washington Hospital Center, Washington, DC, USA
[c] Department of Surgery, Hospital of University of Pennsylvania, Philadelphia, PA, USA
[d] Department of Cardiac Anesthesia, Johns Hopkins School of Medicine, Baltimore, MD, USA

* Corresponding author. Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, 200 Lothrop Ave., Pittsburgh, PA 15213, USA. Tel: +1-734-678-8693; e-mail: jhayanga@me.com (J.W.A. Hayanga).

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Abstract

OBJECTIVES: We sought to evaluate the effect of centre volume on survival when extracorporeal membrane oxygenation (ECMO) is used as a bridge to lung transplantation (LTx).

METHODS: We performed a retrospective analysis of the United Network for Organ Sharing data on adult lung transplantations performed between 2000 and 2014. Centres were categorized based on volume of transplants into low-, medium- and high-volume centres (1–5, 6–15 and >15, respectively). Baseline characteristics were assessed and a Kaplan–Meier analysis was used to estimate survival with log-rank test. We used multivariate Cox regression analysis to estimate the risk of post-transplant 1-year mortality between centres.

RESULTS: A total of 342 adult recipients were bridged on ECMO. Of these recipients, 88 (25.7%) were bridged in low, 89 (26%) in medium and 165 (48.2%) in high-volume centres. Patients in medium-volume centres were more likely to be older compared with those in low-volume and high-volume centres with a median age of 56, 46 and 49 years, respectively. High-volume centres reported the highest proportion (94.6%) of bilateral lung recipients, followed by low-volume (86.4%) and medium-volume centres (77.5%). The 30-day survival for the three groups was similar but 1-year survival was higher in high-volume centres (80.8) compared with medium-volume centres (70.0%) and low-volume centres (61.9%). The risk of 1-year mortality in low-volume centres was higher compared with high-volume centres in adjusted analysis (hazard ratio 2.74, 95% confidence interval 1.61–4.68, $P = 0.01$).

CONCLUSIONS: Lowest volume centres have lowest survival and there exists a volume threshold at which better outcomes are achieved.

Keywords: Extracorporeal membrane oxygenation • Volume • Lung transplantation

INTRODUCTION

The acute management of the decompensating patient pretransplantation has evolved during recent years and extracorporeal support is now increasingly being offered as a bridge to lung transplantation (LTx) [1]. Usage of extracorporeal membrane oxygenation (ECMO) has escalated over the past 15 years and survival has also correspondingly improved [1–3]. There is growing evidence of improved efficacy and safety of contemporary ECMO that has further solidified its position as a therapy for end-stage lung disease as well as a bridge to transplantation [1, 4]. Using a time series analysis of national data from the USA, we recently reported a 50% improvement in the survival of patients bridged to LTx using ECMO between 2000 and 2011, representing a considerable narrowing of the gap in survival [1].

Over the past decade, an entire body of literature has linked high volume to improved outcomes in the context of complex surgical procedures [4–12]. LTx falls within the same domain as a complex procedure, and theoretically subject to the same inverse volume-outcome paradigm. Weiss *et al.* reported a 2% increase in mortality with every percentage decrease in LTx centre volume in the USA, where median institutional volume is 9.4 procedures annually [4]. This concept has gained such traction that the majority of payors and the Centers for Medicare and Medicaid use centre volume as a criterion for reimbursement, and the Joint Commission and American Heart Association use it for the designation of 'center of excellence' [13, 14].

With the knowledge that variability exists in performance metrics across transplant centres, and with the added complexity of ECMO administration, we hypothesized that the gains in survival with the

use of ECMO are not uniformly observed across the spectrum of volume. We thus sought to evaluate whether centre volume exerts an effect on survival when ECMO is used as a bridge to LTx.

METHODS

We retrospectively examined the Scientific Registry of Transplant Recipients (SRTR) data files from the United Network for Organ Sharing (UNOS) database to identify recipients who had undergone LTx between 2000 and 2014. This database maintains data elements reflecting donor characteristics, pretransplant recipient characteristics and follow-up characteristics of post-transplant recipients. We included all consecutive first-time adult lung transplant recipients, ≥18 years of age who were bridged on ECMO prior to LTx between January 2000 and December 2014. We excluded those who underwent retransplantation or who received multiple organ transplants. Both patient-level data and transplantation centre data were provided in a de-identified format.

Transplant centres were categorized into tertiles based on the volume of patients bridged on ECMO prior to LTx during the 15-year study period, namely 'High volume' (>15), 'Medium volume' (6–15) and 'Low volume' (1–5). We calculated centre volume after examining all adults who met the inclusion criteria and were supported on ECMO prior to successful LTx. We then compared the groups using preselected recipient, donor and transplant-related characteristics, which included baseline demographic data and clinical descriptors such as primary pulmonary diagnosis, body mass index, renal function, common comorbidities and type of LTx. The main outcome of interest was the difference in survival between the two groups.

Statistical analysis

Descriptive statistics were evaluated and expressed as a mean ± standard deviation for normally distributed continuous variables, median (25th–75th percentiles) for non-normally distributed continuous variables, and percentage for categorical variables at baseline. Difference among groups was tested using a one-way analysis of variance with Bonferroni correction and a Kruskal–Wallis test for normally and non-normally distributed continuous variables. Fisher's exact test was used for categorical variables. We used Kaplan–Meier analysis to estimate patient survival rate at 30 days and at 1 year, for each category of centre, and the differences in survival rate were compared using a log-rank test, taking into consideration time spent on the waiting list. We repeated the Kaplan–Meier analysis after stratifying the cohort into two groups, pre- and post-introduction of the Lung Allocation Score instituted in May 2005. This served to highlight any difference in trends in survival among recipients occurring after the introduction of the Lung Allocation Score. A multivariate Cox proportional hazard model was fitted using recipient-, donor- and transplant-related variables to establish the association between centre volume and the risk of 1-year mortality. Variables with biological plausibility, those significant in univariate analysis and with proven literature support, were included in the multivariate model. This included recipient age, gender, pulmonary diagnosis, year of transplantation, ABO mismatch, bilateral lung transplant and graft ischaemic time. All analyses were performed using Stata 12.0. Statistical tests were two-sided and *P*-values <0.05 were considered statistically significant.

RESULTS

Overall, 414 adults were bridged on ECMO to LTx. A total of 72 of these recipients underwent retransplantation or received multiple organs and thus did not meet inclusion criteria. All the recipients studied survived to LTx with death recorded only during or after the procedure. Of the 342 recipients, 88 were bridged to transplantation using ECMO in low-volume centres, 89 in medium-volume centres and 165 in high-volume centres. Of the 49 centres studied, 35 were designated as low-volume centres, 9 as medium-volume centres and 5 as high-volume centres. The mean and median numbers of LTx procedures performed across centres were 6.79 and 3 respectively during the study period. In all, 22 LTx procedures were performed in the pre-Lung Allocation Score era and the remaining 320 in the post-Lung Allocation Score era.

Table 1 shows the baseline characteristics of the recipients. Those transplanted in medium-volume centres were more likely to be older compared with low- and high-volume centres with a median age of 56, 46 and 49 years, respectively. The three groups also differed by the proportion of patients who were offered bilateral lung transplants. High-volume centres recorded the highest proportion (94.6%) followed by low-volume (86.4%) and medium-volume centres (77.5%). The mean ischaemic time for high-volume centres was significantly higher than the other categories of centres (6.6 h). There was no difference in the mean ischaemic time between medium-volume and low-volume centres (5.2 and 5.6 h, $P = 0.56$). The three groups were similar by gender, race, renal function, body mass index, pulmonary diagnosis of recipients, donor age, donor smoking status, proportion with donor–recipient ABO mismatch, proportion of diabetics and duration on wait-list.

Survival estimates from the Kaplan–Meier analysis after 30 days were 81.6, 89.8, 89.7%, respectively, in low-, medium- and high-volume centres. In the same vein, 1-year survival rates for the three categories of patients were 61.9, 70.0 and 80.8%, respectively, for low-, medium- and high-volume centres (see Fig. 1). The 1-year survival in the pre-Lung Allocation Score era for low-volume centres, medium-volume centres and high-volume centres were 50, 78.5 and 75%, respectively. In the post-Lung Allocation Score era, the 1-year survival for low-, medium- and high-volume centres were 80.8, 67.6 and 63.7%, respectively.

In unadjusted and adjusted Cox regression models, low-volume centres had a significantly higher risk of 1-year mortality compared with high-volume centres [hazard ratio (HR) 2.30, 95% confidence interval (CI) 1.39–3.81, $P = 0.001$ and HR 2.74, 95% CI 1.61–4.68, $P = 0.01$, respectively]. No significant difference was observed when medium-volume centres were compared with high-volume centres in both unadjusted (HR 1.51, 95% CI 0.88–2.60, $P = 0.14$) and adjusted analyses (HR 1.07, 95% CI 0.58–1.98, $P = 0.83$) (Table 2).

DISCUSSION

Recipients bridged to transplantation on ECMO in low-volume centres were found to have the lowest survival. This was observed despite the fact that high-volume centres tolerated longer ischaemic times with equivalent survival in both medium-volume centres and high-volume centres. This finding may be explained by the presence of an existing adult ECMO programme, which would provide the necessary skilled personnel and experience to best support the LTx programme.

Table 1: Donor-, recipient- and transplant-related characteristics by centre volume category

	Low volume (1–5) (n = 88)	Medium volume (6–15) (n = 89)	High volume (>15) (n = 165)	P-value
Recipient				
Age (years)	46 (28–59)	55 (42–61)	49 (34–57)	<0.001
Male (%)	46/88 (52.3)	58/89 (65.2)	99/165 (60.0)	0.22
White (%)	71/88 (80.7)	76/89 (85.4)	141/165 (85.5)	0.08
Body mass index (kg/m^2)	25.0 (5.8)	24.9 (4.6)	24.3 (4.9)	0.45
Diabetes (%)	23/88 (26.1)	26/86 (30.2)	44/162 (27.2)	0.82
Diagnosis				
Idiopathic pulmonary fibrosis	30/88 (34.1)	36/89 (40.5)	67/165 (40.6)	0.06
COPD/emphysema	4/88 (4.6)	12/89 (13.5)	8/165 (4.9)	
Other	54/88 (61.4)	41/89 (46.1)	90/165 (54.6)	
Renal function				
eGFR < 60 ml/min/1.73 m^2	12/88 (13.6)	17/89 (19.3)	19/165 (11.5)	0.1
eGFR between 60 and 90 ml/min/1.73 m^2	20/88 (22.7)	23/89 (26.1)	28/165 (17.0)	
eGFR > 90 ml/min/1.73 m^2	56/88 (63.7)	48/89 (54.6)	118/165 (71.5)	
Donor				
Age	29 (22–47)	32 (23–47)	33 (22–48)	0.71
Smoking history	9/85 (10.6)	11/89 (12.4)	21/164 (12.8)	0.91
Transplant-related				
Graft ischaemic time (h)	5.6 (1.9)	5.23 (1.7)	6.6 (1.5)	<0.001
Waiting time, days (IQR)	18 (7–88)	31 (8–268)	15 (6–75)	0.06
Bilateral transplant (%)	76/88 (86.4)	69/89 (77.5)	156 (94.6)	<0.001
ABO mismatch (%)	4/88 (4.6)	7/89 (7.9)	9/165 (5.5)	0.69

ABO: blood type; eGFR: estimated glomerular filtration rate; IQR: interquartile range; COPD: chronic obstructive pulmonary disease; h: hour.

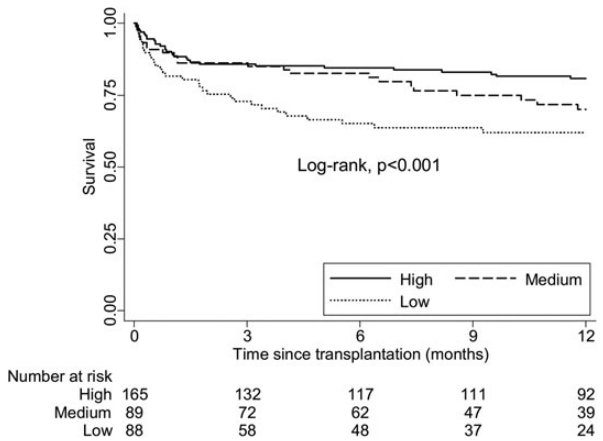

Figure 1: One-year survival between low-, medium- and high-volume centres who bridged patients on ECMO prior to lung transplantation. ECMO: extracorporeal membrane oxygenation.

Table 2: Adjusted and unadjusted Cox regression analysis for 1-year risk of mortality after lung transplantation

	Unadjusted	P-value	Adjusted[a]	P-value
High-volume centre			Reference 1.00	
Medium-volume centre	1.51 (0.88–2.60)	0.14	1.07 (58–1.98)	0.83
Low-volume centre	2.30 (1.39–3.81)	0.001	2.74 (1.61–4.68)	<0.01

[a]Adjusted for recipient age, gender, pulmonary diagnosis, year of transplantation, ABO mismatch, bilateral lung transplant and ischaemic time.

We examined institutional transplant volume rather than volume of patients bridged using ECMO as a matter of practicality. Of the approximate 12 000 patients who underwent LTx from 2000 to 2011, less than 120 (<1%) were bridged to transplantation using ECMO [1]. This implies that individualized institutional numbers would likely be too small to draw any meaningful statistical conclusions if we restricted the volume denominators to only those who were bridged. We thus made the assumption based on the similar statistical behaviour of the two variables which behave as surrogates for each other. Institutions performing the greater number of LTx likely also possess the prerequisite clinical expertise and resources necessary for ECMO, (data-driven protocols, skilled staffing, in-house troubleshooting, etc.). This is, admittedly, a significant logistical undertaking in itself.

The assumption is further supported by the fact that centres that perform the greatest number of LTx also report the most frequent use of ECMO [2, 3]. This is likely because high-volume centres possess more robust denominators that allow them the flexibility to tackle higher risk recipients, which smaller centres may be unwilling to entertain for fear of adverse results, compromising their standing as a transplant centre.

A relationship between improved outcomes and increased volume was observed in this study, and this has also been described in heart transplantation with a threshold below which increased mortality is consistently observed [15]. Weiss *et al.* observed the same trend in LTx, albeit with a weaker predictive power [4]. Similarly, therefore, we hereby report that patients bridged to LTx in low-volume centres have markedly lower survival rates. The reasons are not entirely understood and previous reports have actually shown that complication rates do not differ significantly across the spectrum of centres performing complex procedures. This is likely true for ECMO-related complications [5]. It is likely, however, that higher volume institutions may be better resourced, better staffed

or possess robust recipient selection processes and immunosuppression algorithms. They may perhaps, through the use of pre-existing ECMO programmes, be more appropriately equipped to 'rescue' patients in the context of the complications and morbidities common to ECMO such as haemolysis, infection, bleeding, haemodynamic instability and/or transplantation. The expeditious identification and correction of these complications may play a powerful role in mitigating the morbidity effect on the patient. Further definition in this area is still clearly necessary.

It may be argued that better outcomes in high-volume centres may simply be the result of an increased aggressiveness in utilizing ECMO earlier in the clinical algorithm than in more conservative low-volume centres, suggesting an influence of decision-making algorithms on outcomes. Regardless, the reasons for and against the immediate availability of ECMO are complex and myriad and because this intangible granular detail is not available within the dataset, it is impossible to discern without conjecture. Similar to volume-outcome arguments of the past, therefore, we consider that volume may indeed be a surrogate for other unquantified measures. Published data support the notion that hospital and systems-based resources rather than specific procedural volume that drive improvement in outcomes [4, 16]. We observed no difference in 30-day survival, lending even more credence to the notion that there is more to this than volume. In the USA, the Centers for Medicare and Medicaid predicate reimbursement on achieving an annual volume of 10 LTx. Below this threshold, there exists a reportedly 60% increase in mortality [4]. Low-volume centres, and particularly those without ECMO programmes, assume non-trivial additional risk by bridging patients on ECMO—a risk that in the context of increased mortality could theoretically jeopardize their accreditation or reimbursement.

One might suggest that our results support regionalization of high-risk LTx services in centres of higher clinical expertise and volume. It is not, however, our intention to make evaluative judgements based solely on volume. This might inadvertently discourage smaller volume centres from listing high Lung Allocation Score recipients, or from using ECMO as a bridge to transplantation. Volume has been decried as a poor surrogate for quality. [16] Indeed, some low-volume centres have excellent results and conversely, some high-volume centres have poor results [4, 17]. In keeping with indictment of volume as a marker for quality, Khuri *et al.*, using National Surgical Quality Improvement (NSQIP) data, showed that no correlation exists between volume and risk-adjusted outcomes, and instead advocated against its use as a quality measure [18]. Furthermore, the C-statistic (which indicates the percentage of time that the model predicts survival) for volume in LTx has been estimated at 53%, signifying a comparatively low explanatory power and emphasizing that other factors beyond merely volume exert an influence on outcomes. Indeed, many critics of the volume-outcome paradigm may go even further to maintain that contemporary institution-specific mortality, rather than volume, is a better predictor of survival. The literature, however, has shown that neither is a perfect predictor of future performance, and even when combined, they explain less than half of hospital-level variation in mortality [8, 16]. Additionally, regionalization is predicated on a significant capital outlay, political will and resource allocation. The discussion of which, however, is outside the scope of this analysis.

Nevertheless, our results highlight an important finding that the use of ECMO as a bridge to LTx in low-volume centres is associated with markedly lower survival despite the fact that high-volume centres transplant higher risk recipients. Further research is required to identify those processes of care, institutional algorithms and pathways used in the high-volume centres that allow for the comparatively increased survival. Once identified, those processes may be disseminated so as to establish benchmarks and initiate quality improvement and performance improvement initiatives that limit variation across the tertiles of volume, which is of particular interest in the context of value-based purchasing.

Our study highlights the complexity of the interaction between volume and ECMO. We seek to point out that there may be lessons to be learned from both sides of the spectrum divide. Furthermore, beyond an isolated threshold of volume, it is likely that the inclusion of other specific quality criteria would provide a more accurate index of performance for ECMO centres. This would not wholly replace the volume as a marker but would provide a more robust measure for both accreditation, standardization and evidence-based practice.

Limitations

This study has several limitations. Firstly, the retrospective use of administrative data exposes the analysis to the inherent risk of bias without the reassurance of accounting for all the possible confounders. Secondly, we are unable to distinguish between those patients who were bridged to transplantation using veno-venous (VV) versus those bridged using veno-arterial (VA) ECMO. Thirdly, without the requisite granular detail, we are unable to quantify the independent effect each variable may exert on outcomes. For example, we were unable to extract information on cannulation techniques or hospital-based policies regarding ECMO use which may partially explain our findings. Whereas such quality metrics based on risk-adjusted models that hinge on a single retrospective dataset provide an amount of insight, patients and purchasers may, in the future, show less interest in historical measures and more interest instead in real-time estimates of survival that are likely to be better provided through a score-card system based on composite measures [5, 19–21]. Indeed, there exists a constant threat of bias in the use of national datasets from the multiple unquantifiable factors that pose a perpetual confounding effect.

CONCLUSION AND FUTURE DIRECTIONS

This is the first study to analyse LTx survival post-ECMO bridging across the stratification of procedural volume, and we have identified that survival is lowest in low-volume centres. We do not seek to overstate the value or influence of volume alone. It is likely that centre volume is merely one part of a composite of clinical, procedural, programmatic and logistic measures that influence survival. Instead, we recommend that further research be conducted to allow us greater insight into the most efficacious means of defining and implementing appropriate outcome-based, risk-adjusted measures across the spectrum of volume to improve survival for critically ill patients with end-stage lung disease. In this vein, we continue a quest for granular detail and the accrual of larger clinical experience to further discern centre-specific lessons that may then be dispersed across the spectrum of volume.

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REFERENCES

[1] Hayanga AJ, Aboagye J, Esper S, Shigemura N, Bermudez CA, D'Cunha J *et al*. Extra-corporeal membrane oxygenation as a bridge to lung transplantation: an evolving strategy in the management of candidates with rapidly advancing pulmonary disease. J Thorac Cardiovasc Surg 2015;149:291–6.

[2] Bermudez CA, Rocha RV, Zaldonis D, Bhama JK, Crespo MM, Shigemura N *et al*. Extracorporeal membrane oxygenation as a bridge to lung transplant: Midterm outcomes. Ann Thorac Surg 2011;92:1226–32.

[3] Toyoda Y, Bhama JK, Shigemura N, Zaldonis D, Pilewski J, Crespo M *et al*. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg 2013;145:1065–71.

[4] Weiss ES, Allen JG, Meguid RA, Patel ND, Merlo CA, Orens JB *et al*. The impact of center volume on survival in lung transplantation: an analysis of more than 10,000 cases. Ann Thorac Surg 2009;88:1062–70.

[5] Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009;361:1368–75.

[6] Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I *et al*. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–37.

[7] Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg 2007;245:777–83.

[8] Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349:2117–27.

[9] Morris AM, Billingsley KG, Matthews B, Baldwin LM, Hayanga AJ, Birkmeyer JD. Response: re: residual treatment disparities after oncology referral for rectal cancer. J Natl Cancer Inst 2008;100:1740.

[10] Reames BN, Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and operative mortality in the modern era. Ann Surg 2014;260:244–51.

[11] Meguid RA, Weiss ES, Chang DC, Brock MV, Yang SC. The effect of volume on esophageal cancer resections: what constitutes acceptable resection volumes for centers of excellence? J Thorac Cardiovasc Surg 2009;137:23–9.

[12] Harmon JW, Tang DG, Gordon TA, Bowman HM, Choti MA, Kaufman HS *et al*. Hospital volume can serve as a surrogate for surgeon volume for achieving excellent outcomes in colorectal resection. Ann Surg 1999;230:404–11.

[13] Evans RW. Organ transplantation costs, insurance coverage, and reimbursement. Clin Transpl 1990;343–55.

[14] Evans RW, Manninen DL, Dong FB. An economic analysis of heart-lung transplantation. Costs, insurance coverage, and reimbursement. J Thorac Cardiovasc Surg 1993;105:972–8.

[15] Weiss ES, Meguid RA, Patel ND, Russell SD, Shah AS, Baumgartner WA *et al*. Increased mortality at low-volume orthotopic heart transplantation centers: should current standards change? Ann Thorac Surg 2008;86:1250–60.

[16] Birkmeyer JD, Sun Y, Goldfaden A, Birkmeyer NJO, Stukel TA. Volume and process of care in high-risk cancer surgery. Cancer 2006;106:2476–81.

[17] Hoopes CW, Kukreja J, Golden J, Davenport DL, Diaz-Guzman E, Zwischenberger JB. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. J Thorac Cardiovasc Surg 2013;145:862–8.

[18] Khuri SF, Henderson WG. The case against volume as a measure of quality of surgical care. World J Surg 2005;29:1222–9.

[19] Dimick JB, Pronovost PJ, Cowan JA, Lipsett PA. Complications and costs after high-risk surgery: where should we focus quality improvement initiatives? J Am Coll Surg 2003;196:671–8.

[20] Dimick JB, Staiger DO, Hall BL, Ko CY, Birkmeyer JD. Composite measures for profiling hospitals on surgical morbidity. Ann Surg 2013;257:67–72.

[21] Gonzalez AA, Dimick JB, Birkmeyer JD, Ghaferi AA. Understanding the volume-outcome effect in cardiovascular surgery: The role of failure to rescue. JAMA Surg 2014;149:119–23.