**CONFIDENTIAL**

## U.S. Surgical and Outcome Trends of Thoracic Aortic Surgery

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| 1. | **Project Title** | U.S. Surgical and Outcome Trends of Thoracic Aortic Surgery |
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| 14. | **What Database would you like to query?** | |
| 15. | **Data Requested – Start Date:** | |
| 16. | **Data Requested – End Date:** | |

**TITLE: U.S. Surgical and Outcome Trends of Thoracic Aortic Surgery**

## 1. BACKGROUND:

Acute thoracic aortic dissection (ATAD) is a devastating condition associated with early mortality rate exceeding 50% and high morbidity for those who survive the event (1). Aortic aneurysm is considered the predominating risk factor for ATAD (2). Prophylactic thoracic aortic surgeries are employed for aneurysms above certain diameters with the aim of preventing the occurrence of acute aortic dissection, rupture or sudden death. Operation based on size criteria has been recommended by national and international guidelines since 2001 by European Society of Cardiology and 2010 by the U.S. multidisciplinary task force (3,4). This and the expanded focus on aortic surgery as cardiac surgery sub-specialty is expected to result in increased volume of prophylactic thoracic aortic aneurysm operation. Somewhat contradictory, there are evidences to suggest that the incidence of ATAD has not changed over the last couple of decades. In a recent report from International Registry for Aortic Dissection (IRAD) the overall number of patients presenting with Type A dissection remained stable over the course of 18 years, with decline in operative and non-operative mortalities during this time period (5). Similarly, a nation-wide study conducted in Iceland using a centralized database also demonstrated stable trend in acute thoracic aortic dissection with declining mortalities over the course of the last decade (6). Additional reports are available from Swedish nation-wide study and a population-based study conducted at Oxford (7,8).

The current case volume of thoracic aortic surgeries in the U.S. has not been well studied and trends in surgical outcomes in relation to case complexities remain unknown. Additionally, outcomes related to center-specific case volumes have not been investigated at a national scale, as has been done for other cardiac operations, including mitral valve repair (9) and Norwood operations (10). Although the Society of Thoracic Surgeons national database has provided a report on crude case volume over the last decade (11), this does not take into account for the incomplete penetration of the data, and hence, without a statistical estimation model, the crude case volume would not reflect the actual national trend. Given the paucity of evidence surrounding the national case volume of thoracic aortic surgeries and its temporal trend in the U.S., we aim to evaluate the national trend in case volume, outcomes, and case complexities of thoracic aortic surgeries in the U.S. using the Society of Thoracic Surgeons national database.

## 2. OVERVIEW- Hypothesis/Aim:

Hypothesis: The main hypothesis of the study is that the volume of thoracic aortic surgeries, per capita, in the U.S. has increased significantly over the last 10 years, the case complexity has increased over the period, and the operative mortality of thoracic aortic surgeries has decreased significantly. An additional hypothesis proposes that the operative outcome is associated with center case volumes, with centers that perform higher volumes of thoracic aortic surgeries having improved outcomes compared to those with lower volumes

**Aim 1 Identify and quantify the trend, characteristics, and outcome of thoracic aortic surgeries in the U.S.**: Using the national database of the Society of Thoracic Surgeons (STS), we aim to identify trends in the national case volume of ascending and descending thoracic aortic surgeries between 2000-2015. In addition, we plan to quantify and characterize the trend in perioperative outcomes of thoracic aortic surgeries, case complexity, and risk-adjusted outcomes. In evaluating the trend in the national case volume, we plan to employ adjustments according to changes in the population at-risk, by estimating a scaling factor to account for incomplete data penetration rate, as outlined in the statistical method section.

**Aim 2 Characterize operative outcomes associated with center-specific case volume:** Using the hospital code collected in the STS database, we aim to investigate the association between center case volume and operative outcomes. Multivariate models will be constructed to quantify the risk-adjusted outcome and evaluate whether center case volume remain as an independent predictor of adverse operative outcomes, including mortality and post-operative complications (stroke, reoperation, renal failure, and mechanical ventilation for >24 hours). Using receiver-operator characteristic (ROC) analysis, an optimal cut-off annual case numbers will be identified to stratify the center volume above which is predicted to have an improved operative outcome.

## 3. RESEARCH PLAN

### 3.1 Study patients

3.1.1 Inclusion criteria: Patients who have undergone elective, urgent, and emergent thoracic aortic (ascending or descending) surgeries in the period of 2000 to 2015 in the STS participating centers in the U.S. will be included. Among the database, the U.S. centers will be identified using center address and zip code. The period of 2000 was chosen as the beginning date based on the availability of published patient-level penetration data of the STS national database. In 2000, 51% of the patients who underwent coronary artery bypass grafting data were captured in the STS national database when compared to the Centers for Medicare and Medicaid Services (12). Based on a preliminary estimation, we will evaluate whether the early study period (2000-2005) would provide a robust estimation of the national case volume. If the large proportion of un-reported data proved to interfere with the robustness of the estimation in the early study period, we will then reset the starting year to a later year when both the patient and center-level data penetration is more complete.

3.1.2 Exclusion Criteria: As the STS data houses contributions from small number of international sites, all cases performed in non-U.S. sites will be excluded using the hospital address and zip code. All patients identified to have undergone thoracic aortic surgeries in the U.S. during the study period will be included in the initial analysis. In constructing the multivariate model, patients who are missing critical variables that are required to construct a robust model will be excluded from the final analysis. Univariate comparisons will be employed to evaluate whether the excluded patient cohort differ significantly in baseline characteristics, comorbidities, and operative outcomes compared to those who were included in the final model.

### 3.2 Statistical methods

Outcomes**:** The primary outcome will be defined as the following: operative mortality, defined as in-hospital or 30-day mortality, whichever was greater. Additional outcomes include in-hospital complications (stroke, reoperation for any reason, renal failure, and mechanical ventilation for >24 hours), and a composite end point that consisted of operative mortality and the 4 complications listed above.

Aim1: The temporal trends in the national case volume of thoracic aortic surgeries will be evaluated separately in ascending and descending thoracic aortic surgeries. Within the categories of ascending and descending thoracic surgeries, the groups will be further stratified by emergent vs. elective statuses to construct the table outlining baseline patient data, operative characteristics, and postoperative outcomes. Trends in patient clinical characteristics will be quantified by regression over the 15-year study period. A p value $\leq 0.05$ will be considered statistically significant. Bonferroni correction will be used to control for the family-wise error rate. Baseline patient characteristics and outcomes will be summarized by percentage distribution for categorical variables and by medians and 25th to 75th percentiles for continuous variables. Proportions of missing data will be evaluated and reported. SAS (version 9.4, SAS Institute, Cary, NC) will be used for statistical analysis.

A recently published report evaluating the national STS database demonstrated that the latest patient-level penetration level of the STS data is at 94%, using coronary artery bypass grafting surgery as the surrogate for the overall penetration (12). The penetration level for cases recorded after 2012 (latest available penetration data) will be estimated as 94%, as the penetration level at 2012 was 94% and the penetration level has continuously increased over the years leading to 2012. We will estimate annual national case volume by utilizing a two-step procedure. We start by estimating annual case volumes for all centers that started reporting in 2000 (penetration level of 51%). These initial estimates, covering years 2000 through 2012, can then be aggregated to the state-level. We repeat the same method to estimate state-by-state case volumes for all centers reporting in 2012 (penetration level of 94%) to quantify the growth in case volume for those centers. Secondly, by comparing the overlap year of 2012, when the data is a more accurate representative of the actual national case volume owing to high penetration rate, we will estimate a scaling factor to be applied to the initial estimates to better estimate national case volume over the entire study period.

In order to gain a further insight into the potential cause of temporal changes in case volume, a risk-adjusted estimation of the case volume will be analyzed. Because aortic aneurysm and aortic dissection/rupture affects male and older populations disproportionately, temporal trends in risk-adjusted case volume of thoracic aortic surgeries across gender and age groups will be estimated using national census data, which contains population data specific to gender and age group (13).

In evaluating the temporal trend in case complexity, established cardiac surgical mortality prediction score, EuroSCORE II (14), will be calculated from the following patient variables: age, gender, renal dysfunction, peripheral vascular disease, mobility, previous cardiac surgery, chronic lung disease, active endocarditis, critical preoperative state, insulin-dependent diabetes, New York Heart Association heart failure class, left ventricular function, recent myocardial infarction, pulmonary hypertension, elective/urgent/emergent operative status, and concomitant cardiac operation. Ratio of the actual and estimated rate of mortality, Observed/expected (OE) ratio, will be calculated. In addition, predictors of operative mortality in ascending thoracic aortic surgery that were identified previously using the STS national database (emergent status, pre-operative shock, concomitant cardiac surgery, reoperation, history of stroke, lung disease, chronic kidney disease, and arch involvement) (15) will be evaluated and reported by the 5 stratified era.

In order to evaluate the temporal trend of risk-adjusted operative outcomes, multivariate logistic regression model will be constructed, using variables that serve as a surrogate of case complexities as outlined above. Collinearity will be tested and appropriate exclusion will be applied on as-needed basis.

<u>Aim 2:</u> To evaluate an association between center case volume and outcomes, a multivariate random effects logistic regression model will be constructed to evaluate whether the center case volume persists as an independent risk factor for perioperative mortality, adjusting for potential covariates. These models will consider a random effect for center and fixed effects for hospital volume and other covariates. Random effects take into account for between-center variation in risk-adjusted mortality and adverse event rates due to factors other than volume. The random effects represent any unmeasured factors that might systematically influence the mortality within a hospital. The amount of residual variation in mortality not explained by case volume will be quantified by examining the variance of these random effects.

Average annual hospital case volumes will be categorized into 4 quartiles, with cut points to achieve an approximately equal number of cases in each category. ROC analysis will be conducted to evaluate the center case volume's predictive ability for adverse events, including mortality and stroke. The Yoden index will be utilized to identify the optimal cut-off point of the quartile to identify the case volume above and below which the outcome is estimated to differ.

In addition to categorizing hospital volume, we will perform analyses in which volume will be treated as a continuous variable. A smooth estimate of the relationship between volume and each dependent variable will be obtained by fitting semiparametric logistic regression models. In these models, the effect of center volume will be estimated nonparametrically via smoothing splines. Each of the other explanatory variables will be modeled parametrically. The results of the semiparametric regression analyses will be displayed by plotting risk-adjusted mortality and adverse event rates across categories of center volume.

**3.3 Time table for executing the study**

Month 0: data receipt/initiation of analysis
Month 1: data cleaning (exclusion of non-U.S. centers), evaluation of missing values
Month 1-3: evaluation of temporal trend in case volume, case volume in comparison to population at-risk
Month 4: evaluation of trend in case complexity, risk adjusted operative outcomes, outcomes in relation to center case volumes
Month 5-6: manuscript/abstract preparation and submission

**3.4 Dissemination plans**

The result will be presented at the national Society of Thoracic Surgeons meeting, if accepted. The resulting manuscript will be submitted to the Annals of Thoracic Surgery for a peer-reviewed publication.

**REFERENCES:**

1. Erbel R, Aboyans V, Boileau C et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873-926.
2. Coady MA, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Surgical intervention criteria for thoracic aortic aneurysms: a study of growth rates and complications. The Annals of thoracic surgery 1999;67:1922-6; discussion 1953-8.
3. Hiratzka LF, Bakris GL, Beckman JA et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. J Am Coll Cardiol 2010;55:e27-e129.
4. Erbel R, Alfonso F, Boileau C et al. Diagnosis and management of aortic dissection. Eur Heart J 2001;22:1642-81.
5. Pape LA, Awais M, Woznicki EM et al. Presentation, Diagnosis, and Outcomes of Acute Aortic Dissection: 17-Year Trends From the International Registry of Acute Aortic Dissection. J Am Coll Cardiol 2015;66:350-8.
6. Melvinsdottir IH, Lund SH, Agnarsson BA, Sigvaldason K, Gudbjartsson T, Geirsson A. The incidence and mortality of acute thoracic aortic dissection: results from a whole

nation study. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2016.
7. Olsson C, Thelin S, Stahle E, Ekbom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. Circulation 2006;114:2611-8.
8. Pacini D, Di Marco L, Fortuna D et al. Acute aortic dissection: epidemiology and outcomes. Int J Cardiol 2013;167:2806-12.
9. Gammie JS, O'Brien SM, Griffith BP, Ferguson TB, Peterson ED. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. Circulation 2007;115:881-7.
10. Tabbutt S, Ghanayem N, Ravishankar C et al. Risk factors for hospital morbidity and mortality after the Norwood procedure: A report from the Pediatric Heart Network Single Ventricle Reconstruction trial. The Journal of thoracic and cardiovascular surgery 2012;144:882-95.
11. D'Agostino RS, Jacobs JP, Badhwar V et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2016 Update on Outcomes and Quality. The Annals of thoracic surgery 2016;101:24-32.
12. Jacobs JP, Shahian DM, He X et al. Penetration, Completeness, and Representativeness of The Society of Thoracic Surgeons Adult Cardiac Surgery Database. The Annals of thoracic surgery 2016;101:33-41; discussion 41.
13. United States Census Bureau. Population Estimates, Population Changes, and Components of Change. https://www.census.gov/popest/data/national/totals/2015/index.html. Accessed on Dec 2, 2016.
14. Nashef SA, Roques F, Sharples LD et al. EuroSCORE II. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2012;41:734-44; discussion 744-5.
15. Williams JB, Peterson ED, Zhao Y et al. Contemporary results for proximal aortic replacement in North America. J Am Coll Cardiol 2012;60:1156-62.