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Risk Factors for Mortality after Thoracic Endovascular Aortic Repair

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Risk Factors for Mortality after Thoracic Endovascular Aortic Repair

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B.A., University of Pennsylvania, 2012

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An abstract of
a thesis submitted to the Faculty of the
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Abstract

Risk Factors for Mortality after Thoracic Endovascular Aortic Repair

By Frances Yifan Hu

Objective:
Over the past decade, thoracic endovascular aortic repair (TEVAR) has increased as a treatment option for a variety of aortic pathologies. Despite this rise in the use of thoracic stent grafts, real-world outcomes from a robust, adjudicated, contemporary dataset have yet to be reported. Previous studies have shown peri-procedural mortality rates between 1.5%-9.5% and procedure-related stroke rates of 2.3%-8.2%. With advances in device engineering and increased physician experience, we hypothesized that the rates of these complications would be reduced in a more recent sample set. The purpose of this study was to determine current rate of mortality after TEVAR, identify risk factors that contribute to thirty-day mortality, and develop a simple scoring system that allows for risk stratification of patients undergoing TEVAR.

Methods:
We examined the 30-day mortality rate following TEVAR using the 2013-2014 American College of Surgeons National Surgical Quality Improvement Program database. Patients undergoing TEVAR for all aortic pathology were identified using procedure codes. Bivariate analyses were performed to evaluate the association of pre-, intra- and post-operative variables with 30-day mortality, followed by multivariable logistic analysis using pre-operative variables only, with $P<.10$ as criteria for model entry. The predictive logistic model was internally validated by cross validation. Variables included in the multivariable model were used to develop a risk score.

Results:
Eight hundred twenty-six patients were included. The thirty-day mortality rate was 7.63% (n=63). In regression analysis, mortality was independently associated with age ≥80 years (odds ratio [OR] 2.32, 95% confidence interval [CI] 1.25-4.31), emergency case (OR 2.61, 95% CI 1.39-4.90), ASA classification >3 (OR 2.89, 95% CI 1.34-6.24), transfusion >4 units in the 72 hours prior to surgery (OR 2.86, 95% CI 1.30-6.28), pre-operative creatinine ≥1.8 mg/dL (OR 2.07, 95% CI 1.05-4.08), and pre-operative white blood cell count ≥12 x 10^9/L (OR 2.65, 95% CI 1.41-4.96). Incorporating these factors, a six-point risk score was generated and demonstrated high predictability for overall thirty-day mortality.

Conclusions:
Recent data from a national, retrospective dataset demonstrate that high perioperative mortality and stroke rates have persisted over the last decade. The risk score derived from this dataset is simple and convenient and serves as a prognostic tool in the pre-operative risk stratification of patients being evaluated for thoracic endovascular aortic repair.

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I. INTRODUCTION

Thoracic endovascular aortic repair (TEVAR) has gained popularity as a minimally-invasive treatment option for a range of thoracic aortic pathologies, following U.S. Food and Drug Administration approval in 2005 and numerous prospective non-randomized multi-institutional trials demonstrating reduced or non-inferior morbidity and mortality rates compared with open surgical repair (1–5). Indications for the procedure have expanded from thoracic aortic aneurysm alone to include acute and chronic aortic dissection, penetrating aortic ulcer, ruptured thoracic aortic aneurysm, blunt traumatic aortic injury, and traumatic aortic transection, as it has rapidly become the procedure of choice for treating patients with thoracic vascular disease processes (6–9).

Both stent graft devices and techniques, however, have evolved over the last two decades to continually refine the TEVAR procedure (10). With complication rates remaining high in endovascular repair (11–13), we lack evidence to support a set of defined patient- and procedure-related variables that may be consistently assessed in efforts to reduce perioperative TEVAR morbidity and mortality. To improve outcomes, it is necessary to focus our attention on the most recently available study period during which procedural implementation and eligible patient populations have been largely consistent. The aim of this study was to use the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database from 2013-2014 to identify risk factors associated with thirty-day mortality following thoracic endovascular aortic repair for all thoracic aortic pathology and develop a predictive score for evaluating mortality risk in patients being considered for the procedure.

II. BACKGROUND

The Thoracic Aorta and its Pathology. The thoracic aorta is susceptible to a range of pathologies, including intramural hematomas, penetrating atherosclerotic ulcers, dissections, and blunt aortic injuries (Figure 1A). By far the most common of these disease entities is the thoracic aortic aneurysm (TAA), a localized dilation of either-or both- the ascending and descending aorta, with an incidence of 10.4 per 100,000 person-years (14). While a fraction of TAAs develop as a consequence of a genetic syndrome and have hereditary etiologies, the vast majority occur sporadically and do not yet have clearly defined cellular or molecular mechanisms (15). Proposed factors contributing to the development of a TAA include degeneration of the medial layer of the aortic wall (Figure 1B), high blood pressure, and atherosclerosis, or a build-up of plaque on the walls of the blood vessel leading to the gradual occlusion of the lumen.

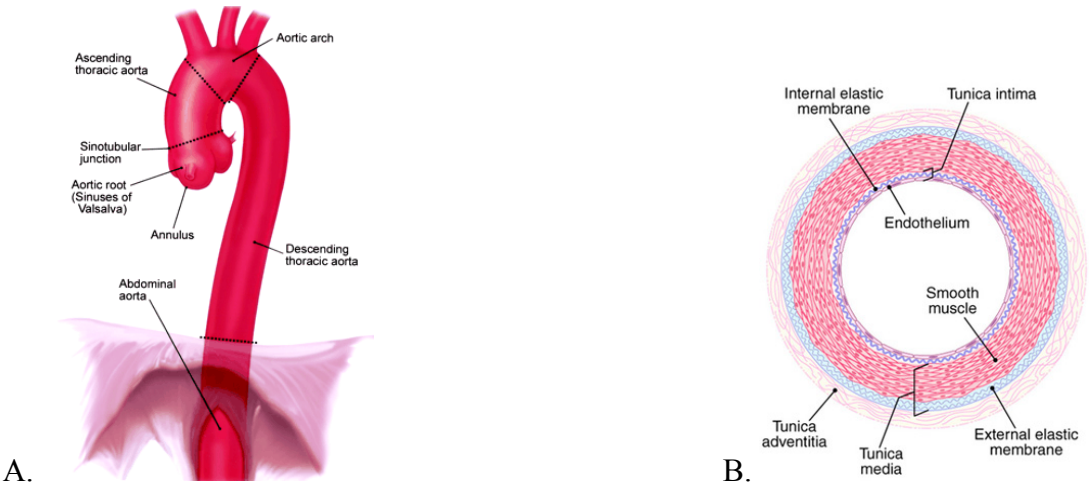

Figure 1. The aorta A. Anatomy of thoracic and proximal abdominal aorta (Image borrowed from Massachusetts General Hospital Thoracic Aortic Center) B. Layers of aorta wall (Image borrowed from University of Texas Health Science Center at San Antonio)

Thoracic aortic aneurysms typically remain asymptomatic and are often detected incidentally on imaging performed for other reasons. One study examining their natural history determined that TAAs grow an average of 0.10 cm each year with the descending thoracic aorta enlarging faster than the ascending aorta (16). Thus, once diagnosed, asymptomatic aneurysms should be monitored with routine imaging studies. The most reliable indicator for operative intervention remains the maximum diameter of the aneurysm (17). The importance of aortic diameter is highlighted by the yearly risk of rupture or dissection, which is 3% at a size of 5.0-5.9 cm but rises to 6.9% at 6.0 cm or greater. When analyzed alone, risk of rupture for aneurysms greater than 6.0 cm is nearly 27 times higher than that for aneurysms 4.0-4.9 cm in size. In patients with a connective tissue disorder, such as Marfan's disease, TAAs have a higher likelihood of dissection at even smaller sizes (18). Based on these findings, a thoracic aneurysm measuring 5.5 cm in the ascending aorta or descending aorta or expanding rapidly (>0.5cm/year) meets criteria for treatment while patients with connective tissue disease, family history, or symptoms qualify for earlier intervention (16,19).

Open Surgical Repair. Traditionally, patients presenting symptomatically or with a TAA meeting size criteria have been offered open surgery to repair the problem. The procedure, which involves a thoracotomy (incision into the chest cavity) and replacement of the aneurysmal segment of aorta with a synthetic graft (Figure 2), should not be considered lightly considering that it is associated with a multitude of complications, including renal failure, spinal cord ischemia, and stroke.

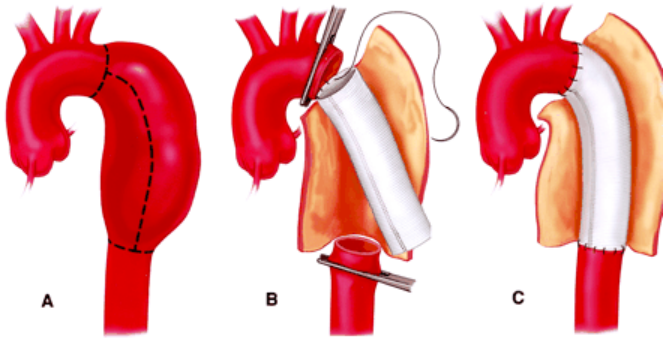

Figure 2. Open surgical repair of descending thoracic aortic aneurysm

(Image borrowed from Massachusetts General Hospital Thoracic Aortic Center)

In a large single-institution case series of open descending thoracic aortic repair, Svensson et al. examined 832 cases performed from 1956-1991 and found a 30-day mortality rate of 8%. They also reported renal failure in 7%, paraplegia/paraparesis in 5%, stroke in 3%, cardiac complications in 10%, and pulmonary complications in 28%. Using Kaplan-Meier analysis for long-term survival, the authors calculated 82% survival at one year and 60% survival at five years (20). Building on these findings, Schermerhorn et al. published population-based outcomes from a later cohort using the Nationwide Inpatient Sample and looking at patients undergoing open repair for descending TAA between 1988 and 2003. In-hospital mortality was 18.3% overall with a lower rate of 10.4% for intact TAAs, and the authors found age, rupture, hospital volume, cerebrovascular disease, chronic renal failure, and absence of hypertension to be independent predictors of mortality. The median length of stay was 17 days, and the overall complication rate for intact TAAs was 42.3% (21).

Thoracic Endovascular Aortic Repair (TEVAR). Despite improvements in critical care and perioperative management, morbidity and mortality still occur at high rates following open surgical repair. For that reason, thoracic endovascular aortic repair (TEVAR), following on the success of stent graft placement in the abdominal aorta (22), presented an attractive alternative for treating thoracic aorta pathologies. The method allows for delivery and controlled placement of a stent through catheter access at a remote vessel, forming a seal between the graft and the aorta wall and excluding the aortic disease process (Figure 3). The thoracic aorta, however, brings a host of its own challenges not previously encountered in the abdominal aorta and requiring additional consideration. This segment of the aorta, located more proximally to the heart, is more compliant and subject to higher displacement forces with each heartbeat (23,24). In 1994, Dake et al. first demonstrated the feasibility of the procedure in 13 patients with descending TAAs (25).

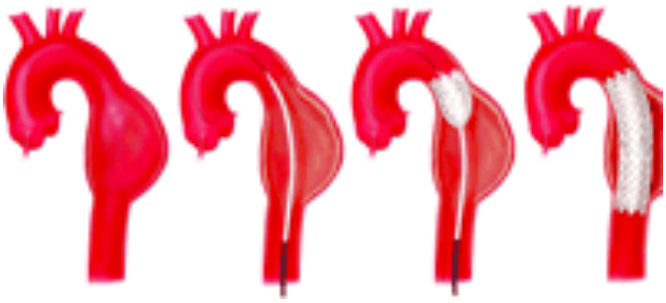

Figure 3. Thoracic endovascular aortic repair of descending thoracic aortic aneurysm (Image borrowed from Massachusetts General Hospital Thoracic Aortic Center)

Clinical Trials Investigating Safety and Effectiveness of Endovascular Repair. The experience of Dake et al. prompted a series of prospective, non-randomized

Investigational Device Exemption (IDE) trials to confirm the safety and effectiveness of TEVAR and evaluate its short-term outcomes. The first commercially available stent graft, the Gore TAG device, was tested in a phase II study at 17 centers across the United States from 1999-2001 in 142 patients with TAAs. Makaroun et al. reported successful device implantation in 98% of patients with 1.5% 30-day mortality, 32% 30-day major adverse event rate, and 3% aneurysm-related two-year mortality (1). The VALOR trial, a prospective, non-randomized study taking place from 2003-2005, examined the 30-day and 12-month results of endovascular repair using the Medtronic Talent stent graft at 38 sites in 195 patients with TAAs and compared them with results from 189 retrospective open surgery patients. Compared with open surgery, endovascular repair showed favorable outcomes with lower rates of all-cause mortality at 30 days (2.1% vs. 7.9%, $p<0.01$), fewer major adverse events at 30 days (41% vs. 84.4%, $p<0.001$), and aneurysm-related mortality at one year (3.1% vs. 11.6%, $p<0.002$) (2). In a prospective non-randomized international trial testing the Cook Zenith TX2 graft from 2004-2006, 160 patients across 42 sites underwent the endovascular procedure for TAAs and large atherosclerotic ulcers, and results were compared with those following open repair in 70 patients. The authors found the 30-day mortality estimate to be non-inferior in the endovascular compared with the open surgery group (98.1% vs. 94.3%) at a 1% significance level. Additionally, the percentage of the TEVAR cohort experiencing a morbid event was lower than that of the open cohort (41.9% vs. 68.6%, $p< 0.01$). At 12 months, the survival estimate from aneurysm-related mortality was similar, 94.2% in the endovascular group and 88.2% in the open group, and the two groups had similar rates of reintervention (4.4% endovascular vs. 5.0 % open, $p=0.74$) (3). These IDE trials

demonstrated that across devices from different manufacturers, the TEVAR procedure had consistent short-term outcomes that were acceptable compared to the previous standard of care.

Long Term Outcomes after Endovascular Repair. Additional studies have reported long-term outcomes through continued follow-up from the industry-sponsored trials. In the first study focusing on long-term outcomes in a large cohort, Fattori et al. published results from 457 patients in the Medtronic Talent Thoracic Retrospective Registry, a database for outcomes in patients with thoracic aortic disease who underwent endovascular treatment with the Medtronic Talent stent graft across seven European centers. They had initially seen in-hospital mortality of 5.1% and in-hospital complications of 12.7%. They were able to find durability of the procedure at long-term follow-up (mean 24 months) with mortality at 8.5% and secondary endoleak in 10.4% of patients. Kaplan-Meier estimates for overall survival were 90.1% at one year and 74.1% at five years (4). Despite a high 43.9% all-cause mortality rate at five-year follow-up in the VALOR trial, the Talent graft sustained its performance with a 96.1% aneurysm-related survival rate, 97.1% freedom from aneurysm rupture, and 81.5% freedom from secondary endovascular procedures at five years (5). At two years, the Gore TAG device demonstrated a 9% rate of endoleak and no difference in survival by Kaplan-Meier analysis when compared with a cohort of 94 concurrent and historical open repair patients (78% vs. 76%, p= 0.48) (26). The findings confirmed the effectiveness of the Gore TAG device for treatment of thoracic aortic aneurysm by showing a decreased rate of aneurysm-related mortality at five years (2.8% vs. 11.7%, p=0.008) (27). Likewise, the

Cook Zenith TX2 trial provided long-term results, finding no significant difference in aneurysm-related mortality (5.9% vs. 12%, p=0.11) or secondary intervention rate (8% vs. 12%, p=0.49%) at five years between patients treated with TEVAR and those treated with open surgery (28). Long-term monitoring informed vascular surgeons about the durability of the grafts, provided rates of complications, gave indications for necessary surveillance protocol, and offered more support to the benefits of TEVAR.

Evolution of TEVAR. With careful assessment of surgical candidates and examination of ensuing complications, modifications have been made to thoracic stent graft design in efforts to better suit the stent graft access, deployment, and device itself to the location and nature of the disease processes being treated. By the time the five-year results of the first ever cohort of TEVAR patients were published in 2004, thoracic stent devices had already progressed to the third generation with smaller delivery systems, better mechanisms for fixation within the aorta, increased flexibility to navigate angulated aortic arch anatomy, and strengthened graft integrity (29). A study at the University of Pennsylvania, intended to guide future device development, reviewed patient characteristics considered in pre-operative evaluation from 2000-2004 and noted specific criteria that necessitated exclusion from TEVAR, such as hostile proximal or distal neck anatomy and unfavorable anatomy making vascular access challenging (30). With respect to the devices themselves, Nienaber et al. observed that the endografts available prior to 2007 were limited by their relative rigidity and their failure to conform and adhere to the wall of the aortic arch (31). The VALOR II trial was a prospective nonrandomized study conducted at 24 sites in the United States from 2006-2009 enrolling 160 patients with

TAAs for endovascular repair using the Medtronic Valiant stent graft, a revised design of the Talent stent graft, and short-term results were measured against those seen in the VALOR trial. Fairman et al. found 3.1% 30-day mortality and non-inferior outcomes at one year with similar all-cause mortality rates between Valiant and Talent cohorts (12.6% vs. 16.1%) (32).

Rapid Adoption of TEVAR. Following approval by the Food and Drug Administration in 2005, the utilization of TEVAR has increased, and individual centers have begun reporting their single institution experiences using TEVAR with indications expanding to include acute and chronic aortic dissection, penetrating aortic ulcer, ruptured TAA, blunt traumatic aortic injury, and traumatic aortic transection (6–9). As studies have repeatedly confirmed the safety of TEVAR and demonstrated post-operative outcomes equivalent or superior to those seen in open surgical repair, endovascular repair has rapidly become the procedure of choice for treating patients with thoracic aorta pathology. At the same time, not a single randomized control trial has been performed, and there have been no direct comparisons of outcomes between patients who were eligible for both procedures and randomized to one treatment. Thus, high level evidence is lacking regarding the effectiveness of TEVAR versus open surgical repair for patients with thoracic aortic pathology (33).

At best, meta-analyses of non-randomized studies have compared endovascular repair to open surgery or compiled data from studies related by a common indication (34–36). This is due to the overwhelming consensus within the vascular community that the newer treatment method far exceeds the conventional option with regard to patient experience

and care. The avoidance of thoracotomy, aortic cross-clamping, and major blood loss are clear advantages in favor of endovascular repair, and clinicians have come to the agreement that a randomized control trial comparing TEVAR to open surgical repair would, in fact, be unethical (37). Considering the fast pace at which both stent graft devices evolve and the criteria for patient eligibility expands, it is unlikely that a randomized control trial would be planned and executed expeditiously enough to remain applicable to the environment in which TEVAR continued to be performed.

Complications in Endovascular and Open Repair. It must be noted, however, that many complications seen in open repair remain significant in endovascular repair and are not to be overlooked (11,12). In a non-randomized retrospective study, Stone et al. reported 7.6% 30-day mortality after TEVAR compared with 15.1% 30-day mortality after open repair ($p=0.09$). The TEVAR group also experienced spinal cord ischemia in 6.7% and stroke in 9.5% compared with 8.6% ($p=0.44$) and 7.5% ($p= 0.62$) in the open surgery group, respectively. Notably, the TEVAR group had a significantly shorter mean total length of stay than the open surgery group (11.0 days vs. 18.76 days, $p= 0.001$) (13). One group comparing outcomes between TEVAR and open surgery for elective descending thoracic and thoracoabdominal aneurysms detected spinal cord injury in 4.3% of endovascular patients compared with 7.5% of open repair patients ($p= 0.08$) (38).

Furthermore, the endovascular procedure is not free from its own risks of morbidity and mortality. Implantation of the stent graft device warrants post-operative surveillance for specific device-related sequelae, including endoleak, device migration, placement of an iliac conduit for vascular access, and celiac artery coverage (39,40). An endoleak may be

characterized by persistent blood flow outside of the stent graft but inside the aneurysmal sac following endovascular repair and falls into one of five categories based on the source and location of the leak with type I, arising at the proximal or distal end of the graft, being the most common (Figure 4) (41). Device migration involves movement of the stent graft either 10mm proximally or distally and could result in endoleak, aneurysm sac expansion, and aneurysm rupture. Placement of an iliac conduit involves an adjunctive open surgical procedure to create a direct connection to the common iliac artery via a synthetic graft and creates additional risks for the patient. The conduit bypasses severe stenosis or tortuosity of the common femoral artery or common iliac artery, limiting or preventing access by catheters and stent devices. Unplanned coverage of celiac artery, a major artery supplying blood to numerous critical organs in the abdomen, could lead to ischemia and require re-intervention following the initial TEVAR procedure.

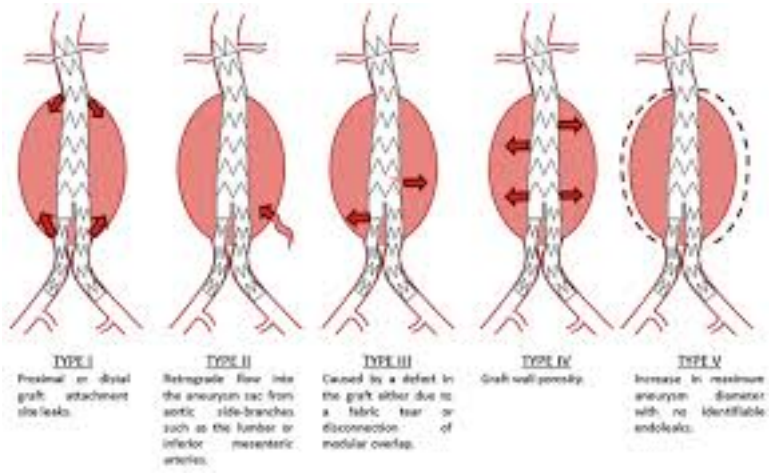

Figure 4. Classification of endoleaks. Type I endoleaks are caused by leakage from either the proximal or distal anchoring points. Type II endoleaks result from continued perfusion of the aneurysm by smaller side arteries. Type III endoleaks are caused by leakage at points of overlap between stent graft pieces. Type IV endoleaks occur when

blood flowing through the stent graft lumen escapes through the stent material into the aneurysm sac. Type V endoleaks are identified as an increase in aneurysm sac diameter with no identifiable cause.

(Image borrowed from England A, McWilliams RG. Endovascular Aortic Aneurysm Repair. *The Ulster Medical Journal.* 2013;82(1):3-10.)

In a retrospective study using data from patients enrolled in the Gore TAG and Medtronic Talent device trials, Parmer et al. evaluated the incidence of endoleaks and factors contributing to their occurrence. They were detected in 29% of patients, and authors found the following variables to be predictive: male sex, larger aneurysm size, length of aorta treated by stent graft, increasing number of stents used (42). The VALOR II trial had stent graft migration in 2.9% and endoleak in 13.0% (32). Stone et al. found endoleaks in 13.3% of patients with 42.9% being type I and requiring reintervention (13).

Risk Factors for Poor Outcomes after TEVAR. Given these findings, attention should be directed towards improving the quality of care for patients undergoing the preferred endovascular procedure. In efforts to anticipate and minimize complications following TEVAR specifically, numerous studies have examined risk factors that could be identified and potentially modified in patients pre-operatively. One study looked at acute kidney injury and found saccular aneurysm pathology, presentation with non-traumatic aortic rupture, need for aortic arch repair, and need for red blood cell transfusion to be risk factors (43). Also, during endovascular repair, achieving an adequate proximal landing zone often requires partial or complete coverage of the left subclavian artery by

the stent graft, reducing outward blood flow to the left vertebral artery and raising awareness for post-operative stroke monitoring. Upon investigation, Gutsche et al. found a history of prior stroke to be predictive of perioperative stroke after TEVAR but did not see an association with coverage of the left subclavian artery or carotid-to-subclavian bypass (44). In contrast, Patterson et al. did identify coverage of the left subclavian artery without revascularization as a risk factor for stroke along with history of stroke, female gender, renal insufficiency, and requirement for two or more devices (45). A group at Harbor-UCLA was unable to identify any significant risk factors for stroke due to low incidence in their cohort following the procedure but found vascular access through an iliac conduit and occlusion or exclusion of the hypogastric artery to be risk factors for spinal cord ischemia (6). Schlosser et al. identified pre-operative renal insufficiency alone to be a risk factor for spinal cord ischemia in patients undergoing TEVAR after previous abdominal aortic aneurysm surgery (46). Yet, Scali et al. were able to incorporate five variables (age, aortic coverage length, COPD, chronic renal insufficiency, and hypertension) into a predictive equation for spinal cord ischemia (47).

Finally, mortality is always an outcome of interest following surgical intervention and has consequently been the outcome of interest for many studies investigating TEVAR patients. Risk factors identified have been as varied as the combined endpoint of perioperative myocardial infarction and neurologic injury, significant comorbidity burden, aortic pathology, persisting type I and III endoleaks, and emergency TEVAR (6,12,48,49). Schechter et al. published preliminary results that frailty, as measured by total psoas volume, was not a significant predictor of 30-day or one-year outcomes, including mortality, major morbidity, and discharge to a facility (50). Marrocco-

Trischitta et al. reported that glomerular filtration rate was a more accurate predictor of 30-day mortality than serum creatinine with a rate <60 ml/min increasing risk of death ten-fold in comparison to that >60 ml/min (51). In a retrospective analysis performed at the University of Florida using data from 2000-2010, authors found that age >70 years, adjunctive intra-operative procedures, peripheral artery disease, coronary artery disease, and chronic obstructive pulmonary disease were all predictors of one-year mortality following TEVAR, while hyperlipidemia was protective (52).

Though several studies on predictors for mortality have been published from single centers, evidence drawn from multi-institutional validated data remains limited. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database provides a large and systematically reviewed patient series for thoracic aortic pathologies. By gathering data from multiple medical centers across geographical regions and with varied clinical volume, it offers a comprehensive compilation of patient outcomes after TEVAR that are likely to be more representative than those reported from specialized vascular surgery centers. The ACS NSQIP database contains many modifiable patient and procedure-related characteristics and has been previously used to generate a universal surgical risk calculator, as well as several procedure-specific risk calculators (53–57).

To date, a number of vascular studies focusing on TEVAR have made use of the NSQIP database (58,59). One group used NSQIP to investigate the role of gender on TEVAR outcomes. As part of their analysis, they looked at only a few possible predictors of 30-day mortality and reported age, emergency surgery, and need for iliac artery exposure to be independently associated with higher mortality rates (60). Meanwhile, Kilic et al.

performed a comprehensive examination of pre-operative variables that played a role in perioperative mortality after TEVAR and combined ten risk factors into a risk score (61). Knowing that patients with thoracic aortic pathology often manage several medical comorbidities, the benefits of any invasive procedure must be carefully weighed against the risks. TEVAR, in particular, warrants careful attention as stent grafts and their accompanying endovascular techniques have evolved significantly since the first generation to improve device durability and accommodate more challenging patient anatomy. By narrowing the date range for the study, we aimed to obtain a recent patient cohort for which TEVAR implementation has been more consistent so that we may identify reliable patient-related and procedure-related risk factors. This study utilized the ACS NSQIP database to perform an in-depth investigation of risk factors contributing to 30-day mortality following TEVAR for thoracic aortic pathology from 2013-2014 and develop a predictive risk score.

III. METHODS

Specific Aims.

Aim 1. To identify risk factors associated with 30-day mortality following thoracic endovascular aortic repair

Aim 2. To develop a risk score to stratify patients being evaluated for thoracic endovascular aortic repair

Data Acquisition. Patients undergoing TEVAR for all aortic pathology were identified from the 2013-2014 ACS NSQIP Participant Use Files using Current Procedural Terminology (CPT) codes, 33880 and 33881. Demographic and pre-operative through thirty-day post-operative data are prospectively collected by trained surgical clinical reviewers and entered into the secure NSQIP database at each participating hospital. The annual participant use file user guide provides standardized definitions for each variable, and the data are abstracted by examining patient medical records, communicating with treating physicians, and directly contacting patients as necessary (62). The 2013 and 2014 participant use files contained adult patient-level data from 435 and 517 hospitals, respectively. For HIPAA-compliance, the distribution of cases per participating center is not disclosed. There were no exclusion criteria for this retrospective cohort study. The patient data are de-identified; informed consent was not required, and the study was determined to be exempt from Institutional Research Board review.

Data Collection. Demographic and pre-operative variables considered included age, sex, race (Caucasian or not Caucasian), transfer status (from home or not from home), emergency case, American Society of Anesthesiologists (ASA) classification (I/II/III, normal healthy or mild systemic disease or severe systemic disease that is not a constant threat to life, or IV/V, severe systemic disease that is a constant threat to life or moribund), diabetes mellitus (no or oral medication/insulin dependent), smoking status (within one year of operation), dyspnea (none or moderate exertion/at rest), ventilator dependence (ventilator-assisted respiration in the 48 hours prior to surgery, excluding treatment of sleep apnea with CPAP), chronic obstructive pulmonary disease, congestive heart failure, hypertension requiring medication, dialysis, disseminated cancer, weight loss (>10% in last 6 months), steroid use, bleeding disorder, functional status prior to surgery (independent or partially/totally dependent), pneumonia, urinary tract infection, transfusion (>4 units within 72 hours before surgery), pre-operative wound infection, systemic sepsis (systemic inflammatory response syndrome or sepsis/septic shock), pre-operative white blood count, pre-operative hematocrit, pre-operative creatinine, and pre-operative albumin. Age was initially grouped into smaller bins (<60 years, 60-69 years, 70-79 years, or ≥80 years). The ranges for the latter two bins were intentionally selected for clinical interest as vascular surgeons are increasingly faced with making treatment decisions for older patient populations (63–65). The variable was later dichotomized into two groups only (<80 years or ≥80 years). The pre-operative lab values white blood count and creatinine were also first grouped into smaller bins (≤12 x 10^9/L, 12.1-13.0 x 10^9/L, 13.1-14.0 x 10^9/L, 14.1-15.0 x 10^9/L, >15 x 10^9/L; and <1.20 mg/dL, 1.20-1.39 mg/dL, 1.40-1.59 mg/dL, 1.60-1.79 mg/dL, ≥1.8 mg/dL, respectively). These were later

combined into two categories for each variable ($\leq 12 \times 10^9$/L or $>12 \times 10^9$/L for white blood count; <1.8 mg/dL or ≥1.8 mg/dL for creatinine (19)).

Intra-operative variables considered included surgical specialty, principal anesthesia technique, left subclavian coverage, thoracic aortic dissection, and wound classification (clean or clean-contaminated/contaminated/dirty-infected). Post-operative variables considered included superficial surgical site infections, pneumonia, unplanned intubation, pulmonary embolism, ventilator dependence (>48 hours), acute renal failure, progressive renal insufficiency, urinary tract infection, cerebrovascular accident, cardiac arrest requiring cardiopulmonary resuscitation, myocardial infarction, transfusions (intra-operative or post-operative), deep venous thrombosis requiring therapy, sepsis, septic shock, total hospital length of stay, length of stay >30 days, readmission, and unplanned reoperation. The variable, days from operation to death, was used to identify which patients were included in the primary outcome, thirty-day all-cause mortality.

Statistical Analysis. First, all variables considered in our study population were examined in a descriptive fashion. For these descriptive analyses, categorical variables are represented as frequency (%) while continuous variables are reported as mean +/- standard deviation (Table 1). Next, bivariate analyses with the primary outcome of thirty-day all-cause mortality were conducted for pre-, intra-, and post-operative variables using χ^2 test or Fisher's exact test for categorical variables or t-test for continuous variables.

To identify significant predictors for the outcome in multivariable analysis, logistic regression models for thirty-day mortality were constructed. Only pre-operative variables

with the potential to be modified prior to the procedural intervention were considered for model entry while intra- and post-operative variables were not considered. Variables significant at a $P<0.10$ level in bivariate analysis and with less than 5% missing data were eligible for model entry. Model 1 contained only dichotomous variables, and the initial equation for the model is as follows:

logit P(30-day all-cause mortality=1) = β_0 + β_1*Age ≥80 + β_2*Transfer status + β_3*Emergency case + β_4*ASA classification + β_5*Smoking status + β_6*Ventilator dependence + β_7*Dialysis + β_8*Bleeding disorder + β_9*Pre-operative pneumonia + β_{10}*Transfusion + β_{11}*Sepsis + β_{12}*White blood count ≥12 + β_{13}*Hematocrit + β_{14}*Creatinine ≥1.8

Model 2 consisted of both dichotomous variables and categorical variables with more than two groups, which were represented by dummy variables. The second model was constructed to evaluate for a potential linear association between those variables with multiple categories and the outcome or provide data-based justification for a dichotomous classification. The equation for the model is as follows:

logit P(30-day all-cause mortality=1) = β_0 + β_1*Age1 + β_2*Age2 + β_3*Age3 + β_4*Transfer status + β_5*Emergency case + β_6*ASA classification + β_7*Smoking status + β_8*Ventilator dependence + β_9*Dialysis + β_{10}*Bleeding disorder + β_{11}*Pre-operative pneumonia + β_{12}*Transfusion + β_{13}*Sepsis + β_{14}*WBC1 + β_{15}* WBC2 + β_{16}* WBC3 + β_{17}* WBC4 + β_{18}*Hematocrit + β_{19}*Creatinine1 + β_{20}*Creatinine2 + β_{21}*Creatinine3 + β_{22}*Creatinine4,

where age <60 years was the reference category, Age1= 60-69 years, Age2= 70-79 years, Age3= ≥80 years, white blood count ≤12 x 10^9/L was the reference category, WBC1= 12.1-13.0 x 10^9/L, WBC2= 13.1-14.0 x 10^9/L, WBC3= 14.1-15.0 x 10^9/L, WBC4= >15 x 10^9/L, creatinine <1.20 mg/dL was the reference category, Creatinine1= 1.20-1.39 mg/dL, Creatinine2= 1.40-1.59 mg/dL, Creatinine3= 1.60-1.79 mg/dL, and Creatinine4= ≥1.8 mg/dL

The backward selection approach was used with a stay criteria of P<0.10. Variables included in each model were assessed for potential interaction, and additional variables of clinical significance were selected for model entry. The models were evaluated using the c-statistic and the Hosmer-Lemeshow goodness of fit test. Additionally, Model 1 underwent internal validation by leave-one-out cross validation, for which one observation was set aside from the entire study population, and a model was fitted to the remainder of the data. The model was used to predict the outcome for the 'missing' observation, and the process was repeated with each observation in the study cohort.

To generate a clinically applicable risk score, the variables incorporated in the final iteration of Model 1 were used. Points were assigned to risk factors significant at p<.05 based on their parameter estimates, given that a logistic regression model combines parameter estimates additively to determine the effect of predictor variables on the outcome variable. Emphasis was placed on designing a risk score that would be simple and easy to use in a fast-paced clinical setting. Thus, the point value for each variable was derived by rounding its parameter estimate to the closest integer. As a method to allow for moderate differentiation, variables with parameter estimates ranging from X.5-X.7 would be given an additional 0.5 points in the risk score. With all the variables in Model

1 being classified dichotomously, the calculation of the score would not be affected by changes in gradation or severity of a clinical variable. The risk score was used to calculate predicted probabilities for thirty-day mortality for comparison with observed probabilities. Predicted probabilities were plotted against observed probabilities to assess calibration of the model. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

IV. RESULTS

Between 2013 and 2014, a total of 826 patients (441 men, 322 women) underwent TEVAR and were included in the analysis. The mean age was 68.2 ± 12.7 years, and 68.8% of patients identified as Caucasian. Of the procedures performed, 188 (22.8%) were considered emergent while 396 (48.0%) were considered elective, and 211 (25.5%) patients were transferred from a facility other than home. Patient demographics and pre-operative characteristics for the study population are outlined in Table 2. In descending order of frequency, the most common indications for which the procedure was performed are as follows: 334 thoracic aortic aneurysms without rupture (40.4%), 153 thoracic aortic dissections (18.5%), 79 thoracoabdominal aortic aneurysms without rupture (9.6%), 50 thoracic aortic aneurysms with rupture (6.1%), 43 thoracoabdominal aortic dissections (5.2%), 25 abdominal aortic aneurysms without rupture (3.0%), 14 aortic dissections of unspecified site (1.7%), 18 thoracoabdominal aortic aneurysms with rupture (2.18%), and 6 abdominal aortic aneurysms with rupture (0.7%). Patients observed to have abdominal aortic indications were presumed to have thoracic indications with concomitant abdominal indications. TEVAR was performed by a vascular surgeon in a total of 787 (95.3%) cases, and 292 (35.4%) procedures involved coverage of the left subclavian artery (Table 3).

The thirty-day all-cause mortality in this patient population was 7.6% (n=63), with the mortality rate in the subset of patients undergoing elective cases being 2.3% (n= 9). 313 (37.9%) patients experienced at least one post-operative complication (Table 4). The post-operative stroke rate was 4.5% (n=37) while the rate of post-operative acute renal failure was 2.7% (n=22). The median total length of hospital stay was 5 days (IQR 3-10

days). Ninety-two patients (11.1%) were readmitted within thirty days with 69 (8.4%) requiring unplanned reoperation (Table 4).

In bivariate analysis, demographic and pre-operative variables found to be significantly associated with thirty-day mortality included age ≥80 years (P=.033), transfer status (P<.0001), emergency case (P<.0001), ASA classification >3 (P<.0001), ventilator requirement within 48 hours of surgery (P<.0001), dialysis requirement (P=.014), history of bleeding disorder (P=.0078), acute pneumonia (P=.022), transfusion >4 units of packed red blood cells prior to 72 hours before surgery (P<.0001), systemic sepsis (P<.0001), white blood cell count >12 x 10^9/L (P<.0001), decreased hematocrit (P=.0067), creatinine ≥1.8 mg/dL (P=.0046), and decreased albumin (P=.0003) (Table 2). No intra-operative variables were significantly associated with thirty-day mortality in bivariate analysis (Table 3). Patients with any post-operative complication (P<.0001), specifically pneumonia (P=.017), unplanned intubation (P<.0001), ventilator requirement >48 hours (p<.0001), acute renal failure (P=.0007), progressive renal insufficiency (P=.016), cerebrovascular accident (P<.0001), cardiac arrest requiring cardiopulmonary resuscitation (P<.0001), and septic shock (P<.0001), need for intra-operative or post-operative blood transfusions (P<.0001), or unplanned reoperation (P=.0014) had a higher risk of thirty-day mortality, compared to those who did not have the complication (Table 4).

For the multivariable model containing only dichotomous variables (Model 1), fourteen demographic and pre-operative variables met criteria for entry. Backward logistic regression found age ≥80 years (odds ratio [OR] 2.32, 95% confidence interval [CI] 1.25-4.31), emergency case (OR 2.61, 95% CI 1.39-4.90), ASA classification >3 (OR 2.89,

95% CI 1.34-6.24), transfusion >4 units in the 72 hours prior to surgery (OR 2.86, 95% CI 1.30-6.28), pre-operative creatinine ≥1.8 mg/dL (OR 2.07, 95% CI 1.05-4.08), and pre-operative white blood cell count ≥12 x 10^9/L (OR 2.65, 95% CI 1.41-4.96) to be independent predictors of thirty-day mortality (Table 5). This multivariable model performed well, with a c-statistic of 0.81, and the Hosmer-Lemeshow goodness-of-fit test resulted in a non-significant P of .41. Using cross-validation, Model 1 was satisfactory in discrimination with a c-statistic of 0.76.

When using variables with more than two categories to construct a model (Model 2), thirteen demographic and pre-operative variables met entry criteria. Emergency case (OR 2.30, 95% CI 1.20-4.40), ASA classification >3 (OR 2.92, 95% CI 1.33-6.39), history of bleeding disorder (OR 2.16, 95% CI 1.08-4.34), transfusion >4 units in the 72 hours prior to surgery (OR 2.62, 95% CI 1.18-5.82), pre-operative creatinine (1.20-1.39 mg/dL, OR 1.11, 95% CI 0.42-2.94; 1.40-1.59 mg/dL, OR 2.86, 95% CI 1.21-6.72; 1.60-1.79 mg/dL, OR 0.34, 95% CI 0.04-2.73; ≥1.8 mg/dL, OR 2.20, 95% CI 1.03-4.46, relative to ≤1.2 mg/dL), and pre-operative white blood cell count (12.1-13.0 x 10^9/L, OR 1.13, 95% CI 0.23-5.45; 13.1-14.0 x 10^9/L, OR 2.86, 95% CI 0.93-8.75; 14.1-15.0 x 10^9/L, OR 1.50, 95% CI 0.37-6.03; >15.0 x 10^9/L, OR 3.02, 95% CI 1.38-6.61, relative to <12 x 10^9/L) were found to be independent predictors of thirty-day mortality using backward logistic regression (Table 6). For both of the predictors represented with dummy variables, white blood count, and creatinine, the odds ratio values did not correspond to increases in the values of the variables. This multivariable model performed well, with a c-statistic of 0.80, and the Hosmer-Lemeshow goodness-of-fit test resulted in a non-significant P of .94.

To construct a predictive risk score, we examined the parameter estimates for the predictors seen in Model 1. Given that the parameter estimates for all significant variables associated with thirty-day mortality rounded most closely to one, each risk factor was assigned an equal weight, and calculation of the risk score was simplified to the number of risk factors identified by the model present in a given patient, ranging from 0-6. No predictor variables had parameter estimates falling in the range of 1.5-1.7, eliminating the need to assign an additional 0.5 points to any variables included in the risk score. Using logistic regression with number of risk factors as a predictor of thirty-day mortality, the model yielded a c-statistic of 0.801 and demonstrated high predictability for the outcome (OR 2.61, $p<.0001$). Comparing predicted to observed probabilities for the outcome, increasing risk score was correlated with higher rates of thirty-day mortality. When stratified by 0 (n=241), 1 (n=265), 2 (n=179), 3 (n=104), or 4+ (n=37) risk factors, the predicted probability of thirty-day mortality was 1.33%, 3.40%, 8.41%, 19.34%, and 38.49%, respectively (Figure 5). On a plot of predicted versus observed probabilities, the slope of the line of best fit was 0.924 with an intercept of 0.33 and an R^2 value of 0.99, indicating good calibration of the risk score.

V. DISCUSSION

This study examined demographic and pre-operative risk factors for thirty-day mortality after thoracic endovascular aortic repair in 826 patients using the ACS NSQIP database from 2013-2014 and constructed two different multivariable predictive models. Based on the model making fullest use of the data, we developed a six-point user-friendly risk score. In this cohort, all-cause mortality was observed to be 7.6%. Compared to prior studies, minimal change has been seen in the rate of this outcome, which has ranged from 1.5-9.5% in the last decade (13,49,52,66). As diagnostic and treatment strategies advance, the applications of TEVAR continue to change, resulting in a shifting heterogeneous patient population and requiring frequent re-examination of the risk factors employed in the clinical assessment of patients.

Using a recent large real-world dataset, we identified a number of demographic and pre-operative variables that were risk factors for thirty-day all-cause mortality and utilized them to create an easy and practical clinical tool for stratification and counseling of patients under consideration for TEVAR. Through cross-validation, we tested the reliability of Model 1 and showed it to be satisfactory. As additional evidence for the dichotomization of categorical variables in Model 1, we constructed Model 2 using the same set of original variables but multiple categories within certain variables. Despite the minimal difference in discriminatory ability between models, the odds ratios for several dummy variables indicated that those intermediate categories of the multi-category variable were not statistically significant and that the variable did not have a linear relationship with the outcome. We consequently chose to use the variables identified as independent predictors of mortality in Model 1 for development of our risk score.

Importantly, each variable received equal weighting in the calculation of the risk score, allowing for quick application and simplicity of use. Upon plotting predicted and observed probabilities for the outcome against number of risk factors present, we found that the two probabilities correlated well, as we would expect with the appropriate selection of variables for incorporation in our risk score.

Previous studies have identified variables associated with mortality using multivariable models (49,51,52,66). Most recently, Kilic et al. used the 2005-2012 ACS NSQIP database to generate a 30-point composite risk score composed of ten risk factors, including age >70 years, BMI <30 kg/m^2, chronic obstructive pulmonary disease, functional status prior to surgery, pre-operative blood urea nitrogen >25 mg/dL, pre-operative white blood cell count >12 x 10^9/L, emergency case, left subclavian artery coverage, thoracoabdominal extension, and mesenteric debranching (61). This risk score, however, could be cumbersome to apply in a clinical setting, as it requires lengthy examination into a patient's medical record and diagnostic imaging followed by stratification into one of three risk tiers.

Several of the identified risk factors identified in our study are not modifiable, including age and need for a pre-operative transfusion. Nevertheless, it is still important for surgeons to be aware that these variables may result in a higher likelihood of patient mortality. Such recognition could prompt more vigilant monitoring intra-operatively or additional coordinated care efforts by multidisciplinary healthcare providers, especially in cases where the patient required the procedure despite having multiple risk factors present. We also identified several variables that are able to be altered and that offer opportunities for pre-operative optimization. For instance, patients found to have an acute

episode of significantly elevated creatinine level may be medically optimized through hemodialysis, should timing of the procedure allow. Any applied intervention would then have to be investigated to assess its impact on outcomes.

Though many risk factors, varying from older age to emergency case, have repeatedly been associated with thirty-day mortality(60,61), the model we constructed using this contemporary dataset also yielded many different predictors. Of note, we did not find left subclavian artery coverage to be a significant risk factor for mortality, though it has previously been found to be predictive of both stroke and mortality (61,67). Similarly, chronic obstructive pulmonary disease was not significant in bivariate analysis nor did it remain in the multivariable model, unlike prior findings (52,61,66). Our results might suggest that these variables pertaining to more localized processes did not influence the outcome of mortality to the same extent while risk factors frequently representative of systemic alterations in health status, such as elevated white blood cell count or increased red blood cell transfusion requirement, were found to be significant in our sample population.

While our study has contributed to the collection of possible risk factors for thirty-day mortality, we are still unable to confirm that these findings are applicable to other patient cohorts. The lack of consistency in risk factors for mortality found across studies, even those completed with the same database, speaks to the dynamic environment in which TEVAR is being performed (52,60,61). We suspect that the outcomes are influenced by the increasing eligibility of the patient population, the new generations of stent grafts, and the modifications to operating room technique (68–70). Stent graft constructs have become slimmer in profile to facilitate their delivery through narrower blood vessel

lumina and arteries with heavier atherosclerotic disease burden. The stent grafts have been manufactured with less rigid materials, allowing them to be more conformable and form a better seal between the device and the aortic wall, as well as more durable materials, reducing the chances of graft breakdown and need for re-intervention. Additionally, the design and contour of the stent grafts undergo continual adaptation to decrease their likelihood of migration along the aorta after deployment and the possibility of uncovering a portion of the diseased aortic segment. Between 2005 and 2011, the U.S. Food and Drug Administration (FDA) passed approval on four new stent graft designs for treatment of thoracic aortic disease (10). As the technique and devices involved in TEVAR have adapted over time, the applications for the procedure have also expanded. Even within our study period, the conformable Gore TAG device received FDA approval for the new indication of aortic dissection in late 2013, soon followed by the Medtronic Captivia Valiant graft in early 2014. It is likely that studies spanning similar or longer time periods are drawing conclusions from a continually changing patient population. Considering the contrast between predictors identified in our study and those found in other studies looking at mortality, we require additional evidence, ideally from prospective application of our risk score, to evaluate the reliability of our model and substantiate its applicability to diverse patients with indications for TEVAR.

Limitations of the study include those inherent in any retrospective dataset analysis as well as specific constraints associated with the NSQIP database. First, the data are entered by trained clinical reviewers using consistent, yet widely interpretable, variable definitions, and we must allow for errors in completion and accuracy, both in the actual patient medical record and the database. We also acknowledge a potential for inter-

provider variation in procedure designations and coding patterns and an inability to verify patient-level information given the de-identified nature of the database. As an example, a patient with an ICD-9 code denoting thoracic aortic dissection could have a concomitant thoracic aortic aneurysm that would escape capture by the NSQIP database, which allows entry of only one ICD-9 code per hospital encounter. In this instance, the patient would be classified as having one diagnosis without the ability to acknowledge a second diagnosis. Thus, associations estimated with certain variables, including indication for procedure, are subject to misclassification bias and must be interpreted conservatively. Another consideration is that an adjunct procedure performed on any given patient during a separate hospital admission, either as a component of a staged procedure or for a separate indication, could be unaccounted for in the database, resulting in measurement error and thus, information bias. For these reasons, we chose not to evaluate the contribution of adjunct procedures towards or away from the outcomes of mortality. The NSQIP database is limited to thirty-day post-operative data, making investigation of late-onset complications challenging. We selected the primary outcome of thirty-day all-cause mortality, which served as an important and clinically relevant surgical outcome. A vascular-related mortality rate could lend more insight into risk factors having a more direct relationship with the outcome but was not available through our dataset. Furthermore, despite it being a recognized and easily accessible source of data for surgical studies, particularly those involving risk scores (53–57), the NSQIP database lacks many patient- and procedure-related variables pertinent to vascular procedures and required to draw more informed conclusions. These might include characteristics, such as history of aortic surgery, history of arterial bypass, aspirin use, beta-blocker use, statin

use, device manufacturer, device length and diameter, presence of endoleak, number of device pieces used, etc. It is possible that the vascular procedure-targeted NSQIP database, soon to be released, may contain these variables of clinical interest and could serve as a better suited database for the examination of risk factors.

As for strengths, the ACS NSQIP database was the first nationally-validated, risk-adjusted program aimed at improving surgical outcomes. It captures data from hospitals across the United States and offers information about national trends, increasing generalizability of the findings. Selection bias is minimized by the random assignment of patient cases from each participating hospital for data abstraction. Moreover, the database includes rich clinical data drawn directly from patient charts, rather than billing or claims data alone. It collects over 130 variables of clinical interest and includes details as specific as pre-operative laboratory values, which are often overlooked in other large validated databases. The vast majority of variables included in the analysis had no missing values, and more specifically, none of the variables meeting selection for logistic regression modeling had missing values, demonstrating the rigor with which the database is maintained. Additionally, the 'Model 1' we developed had good discrimination in predicting mortality after TEVAR and continued to have acceptable discrimination with cross validation. With regard to clinical application of the 'Model 1' developed, the variables incorporated in the risk score may all be found easily with the quick review of a patient's medical record, so such a pre-operative assessment would be quite feasible.

Future studies should pursue external validation with either a later dataset or an independent multi-institutional dataset containing more anatomic or procedure-focused variables in order to offer a better measure of its utility. It would be less beneficial to

validate the risk score with a retrospective dataset considering the advancing nature of the procedure and the widening contrast between previous populations who underwent TEVAR and patients to be evaluated in the future. Another potential avenue of research would be the application of the validated ACS NSQIP surgical risk calculator to this study population for a comparison of performance between the universal risk score with the one we developed in our study specifically for the TEVAR population (57). McMillan et al. amended the universal surgical risk calculator with the addition of procedure-specific variables for pancreatoduodenectomy and found that the model tailored to the patient population improved prediction of poor outcomes (71). Such an investigation might also be valuable in the TEVAR population. Ideally, the risk score would also be applied prospectively in a clinical setting as patients undergo evaluation for TEVAR, whether it be in the office or in the emergency department, for a current and real-time assessment of its generalizability to all patients being considered for the procedure.

In conclusion, we found that perioperative mortality rate after TEVAR has remained high in our recent nationwide dataset at 7.6%. We also found six variables that were independent predictors of 30-day all-cause mortality. Identification of these risk factors and consolidation of these identified variables into a simple and convenient prognostic tool raises the likelihood that the risk score may be adopted in a clinical context. Moving forward, it may offer an easily-calculated estimate of mortality risk following TEVAR and assist in the pre-operative assessment of a patient's suitability for the procedure. Alternatively, the patient and healthcare team would be cognizant prior to surgery if the patient were considered to be at increased risk for poor outcomes, potentially motivating closer intra- and post-operative monitoring or planning for anticipatory interventions.

Accurate evaluation of patient risk would lead to reductions in avoidable re-interventions and improvements in the quality of outcomes.

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VII. TABLES AND FIGURES

Table 1. Study classification of variables

Categorical Variables	
Demographic	*Intra-operative*
Sex	Specialty
Race	Principal anesthesia technique
Hispanic ethnicity	Left subclavian coverage
	Thoracic aortic dissection
Pre-operative	Wound classification
Transfer status	
Emergency case	*Post-operative*
ASA classification	Complication
Comorbidity	Any
Diabetes mellitus	Superficial surgical site infection
Smoking within one year	Pneumonia
Dyspnea	Unplanned intubation
Ventilator dependent	Pulmonary embolism
Severe chronic obstructive pulmonary disease	Ventilator >48 hours
Congestive heart failure within 30 days	Acute renal failure
Hypertension requiring medication	Progressive renal insufficiency
Currently on dialysis	Urinary tract infection
Disseminated cancer	Cerebrovascular accident
Steroid use for chronic condition	Cardiac arrest requiring CPR
Weight loss >10% within 6 months	Myocardial infarction
Bleeding disorder	Transfusions, intra-operative or post-operative
Functional Status	DVT/thrombophlebitis
Acute Conditions	Sepsis
Pneumonia	Septic shock
Urinary tract infection	Length of hospital stay >30 days
Transfusion >4 units within 72 hours	Any readmission
Open wound or wound infection	Unplanned reoperation
Systemic sepsis	
Pre-operative laboratory values	
White blood count (10^9/L)	
Creatinine (mg/dL)	

ASA, American Society of Anesthesiologists; *CPR*, cardiopulmonary resuscitation; *DVT*, deep vein thrombosis.

Continuous Variables	Continuous Variables
Pre-operative	*Demographic*
Pre-operative laboratory values	Age (years)
Hematocrit (%)	
Albumin[c] (g/dL)	*Post-operative*
	Total length of hospital stay (days)

Table 2. Demographic and pre-operative characteristics in patients undergoing TEVAR from 2013-2014 and bivariate comparisons with 30-day mortality

Characteristic	Study Population (n=826)	30-day Mortality No (n= 763)	30-day Mortality Yes (n=63)	P[a]
Age (years) , *mean ± SD*	68.2 ± 12.7			
18-74, *N (%)*	540 (65.4)	502 (93.0)	38 (7.0)	0.38
75-90+, *N (%)*		261 (91.3)	25 (8.7)	
18-79, *N (%)*	651 (78.8)	608 (93.4)	43 (6.6)	0.03
80-90+, *N (%)*		155 (88.6)	20 (11.4)	
18-59, *N (%)*	188 (22.7)	175 (93.1)	13 (6.9)	0.17
60-69, *N (%)*	217 (26.3)	201 (92.6)	16 (7.4)	
70-79, *N (%)*	246 (29.8)	232 (94.3)	14 (5.7)	
80-90+, *N (%)*	175 (21.2)	155 (88.6)	20 (11.4)	
Sex, *N (%)*				0.28
Male	473 (57.3)	441 (93.2)	32 (6.8)	
Female		322 (91.2)	31 (8.8)	
Race, *N (%)*				0.51
Caucasian	568 (68.8)	527 (92.8)	41 (7.2)	
Not Caucasian		236 (91.5)	22 (8.5)	
Hispanic ethnicity[b], *N (%)*				1.00
Yes	18 (2.2)	17 (94.4)	1 (5.6)	
No		667 (92.8)	52 (7.2)	
Transfer status, *N (%)*				<.0001
From home	615 (74.5)	584 (95.0)	31 (5.0)	
Not from home		179 (84.8)	32 (15.2)	
Emergency case, *N (%)*				<.0001
Yes	188 (22.8)	151 (80.3)	37 (19.7)	
No		612 (95.9)	26 (4.1)	
ASA classification, *N (%)*				
1	2 (0.2)	2 (100.0)	0 (0.0)	<.0001
2	27 (3.3)	27 (100.0)	0 (0.0)	
3	345 (41.8)	336 (97.4)	9 (2.6)	
4	420 (50.8)	376 (89.5)	44 (10.5)	
5	32 (3.9)	22 (68.7)	10 (31.3)	
≤3	374 (45.3)	365 (97.6)	9 (2.4)	<.0001
>3		398 (88.0)	54 (12.0)	
Comorbidity				
Diabetes mellitus, *N (%)*				0.16
Yes	110 (13.3)	98 (89.1)	12 (10.9)	
No	716 (86.7)	665 (92.9)	51 (7.1)	
Smoking within one year, *N (%)*				0.07
Yes	267 (32.3)	253 (94.8)	14 (5.2)	
No		510 (91.2)	49 (8.8)	
Dyspnea, *N (%)*				0.65
Yes	121 (14.7)	113 (93.4)	8 (6.6)	

No		650 (92.2)	55 (7.8)	
Ventilator dependent, *N (%)*				<.0001
Yes	27 (3.3)	18 (66.67)	9 (33.3)	
No		745 (93.2)	54 (6.8)	
Severe chronic obstructive pulmonary disease, *N (%)*				0.73
Yes	144 (17.4)	134 (93.1)	10 (6.9)	
No		629 (92.2)	53 (7.8)	
Congestive heart failure within 30 days, *N (%)*				0.49
Yes	30 (3.6)	27 (90.0)	3 (10.0)	
No		736 (92.5)	60 (7.5)	
Hypertension requiring medication, *N (%)*				0.73
Yes	682 (82.6)	631 (92.5)	51 (7.5)	
No		132 (91.7)	12 (8.3)	
Currently on dialysis, *N (%)*				0.01
Yes	44 (5.3)	36 (81.8)	8 (18.2)	
No		727 (93.0)	55 (7.0)	
Disseminated cancer, *N (%)*				1.00
Yes	4 (0.5)	4 (100.0)	0 (0.0)	
No		759 (92.3)	63 (7.7)	
Steroid use for chronic condition, *N (%)*				0.16
Yes	47 (5.7)	41 (87.2)	6 (12.8)	
No		722 (92.7)	57 (7.3)	
Weight loss >10% within 6 months, *N (%)*				0.35
Yes	16 (1.9)	14 (87.5)	2 (12.5)	
No		749 (92.5)	61 (7.5)	
Bleeding disorder, *N (%)*				0.008
Yes	101 (12.2)	86 (85.1)	15 (14.9)	
No		677 (93.4)	48 (6.6)	
Functional status, *N (%)*				0.33
Independent	791 (95.8)	732 (92.5)	59 (7.5)	
Not independent		31 (88.6)	4 (11.4)	
Acute Conditions				
Pneumonia, *N (%)*				0.02
Yes	15 (1.8)	11 (73.3)	4 (26.7)	
No		752 (92.7)	59 (7.3)	
Urinary tract infection, *N (%)*				0.27
Yes	4 (0.5)	3 (75.0)	1 (25.0)	
No		760 (92.5)	62 (7.5)	
Transfusion >4 units prior to 72 hours, *N (%)*				<.0001
Yes	42 (5.1)	29 (69.0)	13 (31.0)	

No		734 (93.6)	50 (6.4)	
Open wound or wound infection, *N (%)*				0.32
Yes	15 (1.8)	13 (86.7)	2 (13.3)	
No		750 (92.5)	61 (7.5)	
Systemic sepsis, *N (%)*				<.0001
None	748 (90.6)	704 (94.1)	44 (5.9)	
SIRS, sepsis or septic shock		59 (75.6)	19 (24.4)	
Pre-operative laboratory values				
White blood count (10^9/L), *mean ± SD*	8.9 ± 4.1	8.6 ± 3.7	13.0 ± 6.4	
≤12, *N (%)*	697 (84.4)	661 (94.8)	36 (5.2)	<.0001
12.1-13.0, *N (%)*	28 (3.4)	26 (92.9)	2 (7.1)	
13.1-14.0, *N (%)*	28 (3.4)	23 (82.1)	5 (17.9)	
14.1-15.0, *N (%)*	17 (2.0)	14 (82.4)	3 (17.6)	
>15.0, *N (%)*	56 (6.8)	39 (69.6)	17 (30.4)	
≤12, *N (%)*	697 (84.4)	661 (94.8)	36 (5.2)	<.0001
>12, *N (%)*		102 (79.1)	27 (20.9)	
Hematocrit (%), *mean ± SD*	36.4 ± 5.9	36.6 ± 5.8	34.3 ± 6.1	0.007
Creatinine (mg/dL), *mean ± SD*	1.3 ± 1.2	1.3 ± 1.1	1.7 ± 1.6	
<1.20, *N (%)*	551 (66.7)	521 (94.6)	30 (5.4)	0.0002
1.20-1.39, *N (%)*	88 (10.6)	82 (93.2)	6 (6.8)	
1.40-1.59, *N (%)*	57 (6.9)	46 (80.7)	11 (19.3)	
1.60-1.79, *N (%)*	27 (3.3)	26 (96.3)	1 (3.7)	
≥1.8, *N (%)*	103 (12.5)	88 (85.4)	15 (14.6)	
<1.80, *N (%)*	723 (87.5)	675 (93.4)	48 (6.6)	0.005
≥1.80, *N (%)*		88 (85.4)	15 (14.6)	
Albumin[c] (g/dL), *mean ± SD*	3.4 ± 0.6	3.5 ± 0.6	3.1 ± 0.7	0.0003

TEVAR, thoracic endovascular aortic repair; *ASA*, American Society of Anesthesiologists; *SIRS*, systemic inflammatory response syndrome. [a]Pearson χ^2, Fisher's exact test or unpaired t-test, as appropriate. [b]89 values categorized as 'Unknown' for Hispanic ethnicity. [c]301 values missing for albumin.

Table 3. Intra-operative outcomes in patients undergoing TEVAR from 2013-2014 and bivariate comparisons with 30-day mortality

Characteristic	Study Population (n=826)	30-day Mortality No (n= 763)	30-day Mortality Yes (n=63)	P[a]
Specialty, *N (%)*				0.76
Vascular	787 (95.3)	726 (92.2)	61 (7.8)	
Not Vascular	39 (4.7)	37 (94.9)	2 (5.1)	
Principal anesthesia technique, *N (%)*				0.25
General	802 (97.1)	739 (92.1)	63 (7.9)	
Not general	24 (2.9)	24 (100.0)	0 (0.0)	
Left subclavian coverage, *N (%)*				0.31
Yes	292 (35.4)	266 (91.1)	26 (8.9)	
No	534 (64.6)	497 (93.1)	37 (6.9)	
Thoracic dissection, *N (%)*				
Yes	153 (18.5)	137 (89.5)	16 (10.5)	0.14
No	673 (81.5)	626 (93.0)	47 (7.0)	
Wound classification, *N (%)*				0.20
Clean	815 (98.7)	754 (92.5)	61 (7.5)	
Not clean	11 (1.3)	9 (81.8)	2 (18.2)	

TEVAR, thoracic endovascular aortic repair. [a]Pearson χ^2 or Fisher's exact test, as appropriate.

Table 4. Post-operative outcomes in patients undergoing TEVAR from 2013-2014 and bivariate comparisons with 30-day mortality

Characteristic	Study Population (n=826)	30-day Mortality No (n= 763)	30-day Mortality Yes (n=63)	P[a]
Complication				
Any, *N (%)*				<.0001
Yes	313 (37.9)	257 (82.1)	56 (17.9)	
No		506 (98.6)	7 (1.4)	
Superficial surgical site infection, *N (%)*				1.00
Yes	9 (1.1)	9 (100.0)	0 (0.0)	
No		754 (92.3)	63 (7.7)	
Pneumonia, *N (%)*				0.02
Yes	54 (6.5)	45 (83.3)	9 (16.7)	
No		718 (93.0)	54 (7.0)	
Unplanned intubation, *N (%)*				<.0001
Yes	55 (6.7)	39 (70.9)	16 (29.1)	
No		724 (93.9)	47 (6.1)	
Pulmonary embolism, *N (%)*				1.00
Yes	4 (0.5)	4 (100.0)	0 (0.0)	
No		759 (92.3)	63 (7.7)	
Ventilator >48 hours, *N (%)*				<.0001
Yes	58 (7.0)	41 (70.7)	17 (29.3)	
No		722 (94.0)	46 (6.0)	
Acute renal failure, *N (%)*				0.0007
Yes	22 (2.7)	15 (68.2)	7 (31.8)	
No		748 (93.0)	56 (7.0)	
Progressive renal insufficiency, *N (%)*				0.02
Yes	3 (0.4)	1 (33.3)	2 (66.67)	
No		762 (92.6)	61 (7.4)	
Urinary tract infection, *N (%)*				0.69
Yes	23 (2.8)	21 (91.3)	2 (8.7)	
No		742 (92.4)	61 (7.6)	
Cerebrovascular accident, *N (%)*				<.0001
Yes	37 (4.5)	24 (64.9)	13 (35.1)	
No		739 (93.7)	50 (6.3)	
Cardiac arrest requiring CPR, *N (%)*				<.0001
Yes	38 (4.6)	9 (23.7)	29 (76.3)	
No		754 (95.7)	34 (4.3)	
Myocardial infarction, *N (%)*				0.12
Yes	16 (1.9)	13 (81.2)	3 (18.8)	
No		750 (92.6)	60 (7.4)	
Transfusions, intra-operative or post-operative, *N (%)*				<.0001

Yes	220 (26.6)	179 (81.4)	41 (18.6)	
No		584 (96.4)	22 (3.6)	
DVT/thrombophlebitis, *N (%)*				0.03
Yes	22 (2.7)	18 (81.8)	4 (18.2)	
No		745 (92.7)	59 (7.3)	
Sepsis, *N (%)*				1.00
Yes	16 (1.9)	15 (93.7)	1 (6.3)	
No		748 (92.3)	62 (7.7)	
Septic shock, *N (%)*				<.0001
Yes	15 (1.8)	7 (46.7)	8 (53.3)	
No		756 (93.2)	55 (6.8)	
Total length of hospital stay (days), *median (interquartile range)*	5 (3-10)			
mean ± SD		8.1 ± 9.1	8.1 ± 7.8	0.98
Length of hospital stay >30 days, *N (%)*				0.40
Yes	21 (2.5)	21 (100.0)	0 (0.0)	
No		742 (92.2)	63 (7.8)	
Any readmission, *N (%)*				0.10
Yes	92 (11.1)	89 (96.7)	3 (3.3)	
No		671 (91.8)	60 (8.2)	
Unplanned reoperation, *N (%)*				0.001
Yes	69 (8.4)	57 (82.6)	12 (17.4)	
No		706 (93.3)	51 (6.7)	

TEVAR, thoracic endovascular aortic repair; *CPR*, cardiopulmonary resuscitation; *DVT*, deep vein thrombosis. [a]Pearson χ^2, Fisher's exact test or unpaired t-test, as appropriate.

Table 5. Multivariable associations of demographic and pre-operative variables with 30-day mortality in patients undergoing TEVAR from 2013-2014

Covariate	Odds ratio (95% confidence interval)	P
Age ≥80 years	2.32 (1.25-4.31)	0.008
Emergency case	2.61 (1.39-4.90)	0.003
ASA classification >3	2.89 (1.34-6.24)	0.007
Pre-operative transfusion >4 units within 72 hours	2.86 (1.30-6.28)	0.009
Creatinine ≥1.8 mg/dL	2.07 (1.05-4.08)	0.036
White blood count ≥12x10^9/L	2.65 (1.41-4.96)	0.002

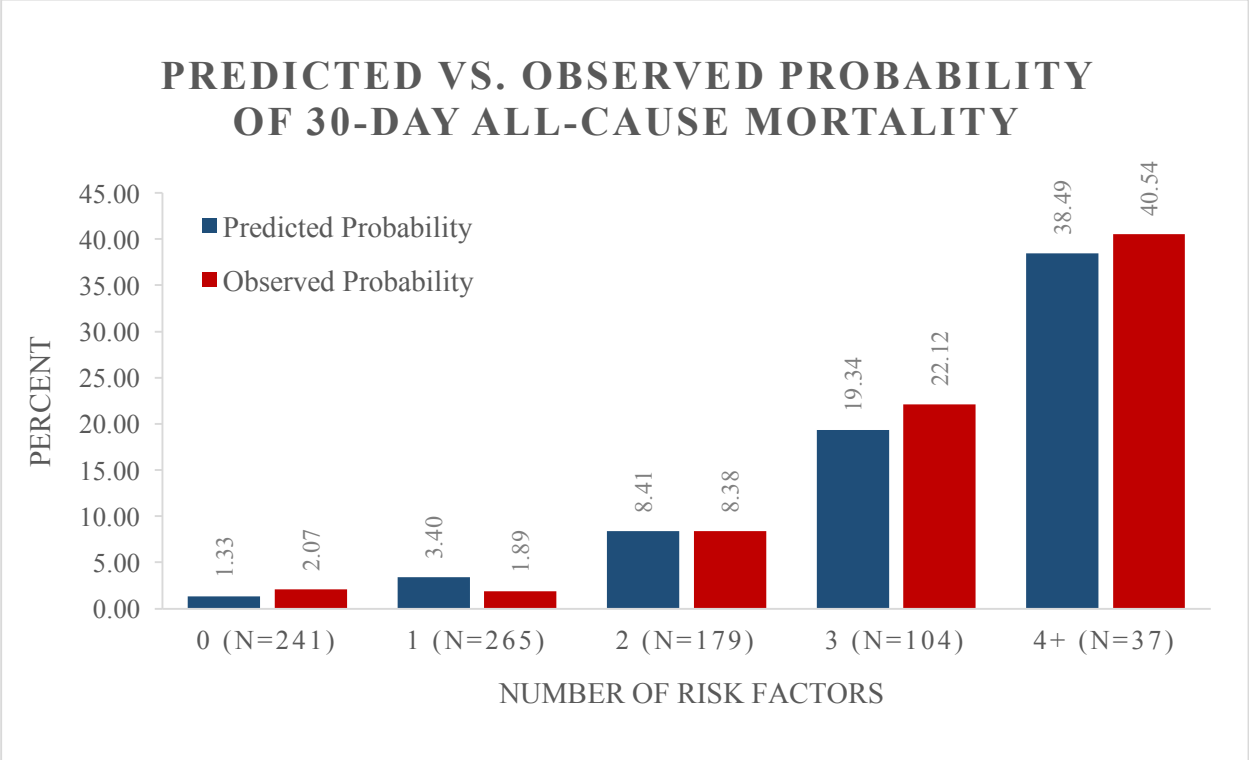
TEVAR, thoracic endovascular aortic repair; *ASA*, American Society of Anesthesiologists.

Table 6. Multivariable associations of multi-category demographic and pre-operative variables with 30-day mortality in patients undergoing TEVAR from 2013-2014

Covariate	Odds ratio (95% confidence interval)	P
Emergency case	2.30 (1.20-4.40)	0.012
ASA classification >3	2.92 (1.33-6.39)	0.007
Bleeding disorder	2.16 (1.08-4.34)	0.030
Pre-operative transfusion >4 units within 72 hours	2.62 (1.18-5.82)	0.018
White blood count, 12.1-13.0 x 10^9/L*	1.13 (0.23-5.45)	0.88
White blood count, 13.1-14.0 x 10^9/L*	2.86 (0.93-8.75)	0.066
White blood count, 14.1-15.0 x 10^9/L*	1.50 (0.37-6.03)	0.57
White blood count, >15.0 x 10^9/L*	3.02 (1.38-6.61)	0.006
Creatinine, 1.20-1.39 mg/dL[#]	1.11 (0.42-2.94)	0.83
Creatinine, 1.40-1.59 mg/dL[#]	2.86 (1.21-6.72)	0.016
Creatinine, 1.60-1.79 mg/dL[#]	0.34 (0.04-2.73)	0.31
Creatinine, ≥1.80 mg/dL[#]	2.20 (1.08-4.46)	0.029

TEVAR, thoracic endovascular aortic repair; *ASA*, American Society of Anesthesiologists.
*compared to white blood count ≤12.0 x 10^9/L.
[#] compared to creatinine <1.20 mg/dL.

Figure 5. Predicted versus observed probability of 30-day mortality in patients undergoing TEVAR from 2013-2014



TEVAR, thoracic endovascular aortic repair.