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Trends Over Time in Incidence of Bicuspid Aortic Valve Patients with Thoracic Aortic Aneurysms in New York

Sarah Marc
sarah.marc@stonybrookmedicine.edu

Jahnvi Bansal
jahnvi.bansal@stonybrookmedicine.edu

Alexander Cove
Alexander.Cove@stonybrookmedicine.edu

Annet Kuruvilla
annetkuruvilla@gmail.com

Joshua Helali
helali.joshua@scrippshealth.org

See next page for additional authors

TITLE: Trends over time in incidence and surgical intervention at index admission for bicuspid aortic valve patients in New York State presenting with thoracic aortic aneurysms

Principal Investigator: Dr. Allison J. McLarty, MD

Co-Principal Investigators: Dr. A. Laurie Shroyer, PhD, MSHA & Dr. Thomas Bilfinger, MD

Medical Student: Jahnvi Bansal, BE

Student Workers: Sarah Marc, BS, Alexander Cove, BS, Mohammad Noubani, BS, Annet Kuruvilla, BS, Sohaib Agha, Josh Helali, Phillp Yeun, Abir Thakur & Ashutosh Yaligar

Co-Investigators: Dr. Henry Tannous, MD, Dr. Aurora Pryor, MD, MBA and Dr. Jie Yang, PhD

Research Question: What are the trends over time associated with number of patients in New York State diagnosed with bicuspid aortic valve (BAV) and/or thoracic aortic aneurysm (TAA) diagnosis in sequence; what are the trends over time of proportion of patients presenting with a ruptured/dissected TAA on admission, and the trends over time for surgical interventions at index admission for such patients? What are the risk factors within the BAV/TAA population that are associated with increased adverse outcomes?

PURPOSE AND SPECIFIC AIMS:

Using publicly available de-identified Statewide Planning and Research Cooperative System (SPARCS) data from 2005 to 2018, this descriptive study seeks to analyze New York State- based data regarding rates of newly diagnosed bicuspid aortic valve (BAV) patients that also have either an ongoing or new diagnosis of thoracic aortic aneurysm (TAA), as well as their subsequent surgical/percutaneous intervention rates. Additionally, clinical risk factors, prior comorbidities, and baseline demographics will be analyzed.

Background and Significance

One of the largest contributors to the overall morbidity and mortality of cardiovascular disease around the world are diseases of the aorta, particularly thoracic aortic aneurysms (TAA) [Ramanath et al., 2009]. As of 2002, the prevalence and incidence of TAA has been reported to be increasing, along with the number of operations done annually [Olsson et al., 2006]. With an increase in TAA incidence over time, and general population increases over time, the number of patients that need to undergo surveillance for potential TAA development increases, and the risk factor profile of patients becomes increasingly complex. BAV, the most frequent adult congenital anomaly, is thought to be associated with an aortopathy prone to early TAA development.

TAAs present in a quiescent fashion; they largely occur in the ascending aorta but can present in any part of the thoracic aorta as well. The most feared complication of TAA is progression to dissection or rupture, a clinical emergency, of which the former is significantly more likely to occur in the BAV patient than the general population. [Goldfinger et al., 2014; Michelena et al., 2011].

At present, diagnosis of thoracic aortic aneurysms is largely incidental, and occurs during routine imaging studies (chest x-ray, CT scan, echocardiogram) that are completed for other reasons [Isselbacher 2005]. CT scan is the most widely used diagnostic modality with which to diagnose TAA, but there are gaps in clinical knowledge regarding the incidence and prevalence of TAAs in any given population. Particularly in the high-risk BAV population, we do not know what a surveillance program in terms of frequency and imaging parameters should look like.

The study's **PICOS** components:

Population: This study's population will include all NYS patients with a new TAA/BAV diagnosis (including all TAA patients and/or all newly diagnosed BAV patients) from January 2005 – December 2018 that did not receive any historical TAA-related and/or BAV-related interventions within 2-years prior to their index admission. The study size was arrived at by including every data point that passes exclusion criteria.

Intervention: Elective admission BAV/TAA surgical procedures versus urgent/emergent admission BAV/TAA procedures

- Primary index hospitalization- intervention versus no intervention
    - Intervention:
        - Open versus percutaneous (May include aortic valve procedure (SAVR/TAVR and or TAA procedure [open, endovascular, or hybrid])

Comparison: Trends over time in prevalence in patients with new BAV and new TAA diagnosis, will be compared to those with a pre-existing BAV with existing TAA, new TAA diagnoses with existing BAV, and concurrent novel BAV/TAA diagnoses. Within these three subgroups, trends over time in adverse outcomes, defined as "bad things happening" which include TAA rupture/dissection, TAA/BAV intervention (percutaneous vs open), and post-operative mortality from said intervention within a two-year period, will be studied. In addition, analysis between the three subgroups, outcome comparisons related to risk factors such as age, sex, race, ethnicity, insurance, and other medical co-morbidities while holding all other risks, BAV/TAA surgical procedures or other treatments will be performed.

Outcomes: The outcomes being studied are: Bad Things Happening (BTH), defined as in-hospital death for any reason in index admission or urgent/emergent surgery in index admission or occurring within a 2 year time period from index admission; and 30-day readmission after initial diagnosis defined as admission within 30 days after discharge from index admission.

Rationale of the Study

For the proper development of a source of information that accurately represents changing trends in TAA incidence, there must be a deeper understanding of the prevalence and outcomes of the issue, in order to further aid clinicians in patient management. As screening modalities have improved, TAAs and BAV patients may be identified sooner without the presence of symptoms. With a better understanding of the speed with which TAA develops and the characteristic other than size, more refined surveillance algorithms can be developed. Using the NYS SPARCS database, analysis of the trends over time with respect to BAV patients and TAA diagnosis, imaging, surgical procedures, and outcomes will illuminate how the prevalence of these combined

diseases has changed and how physicians should adapt current screening recommendations to reflect this shift. Additionally, development of a statistical algorithm to assess risk-factors in BAV and TAA patients will be done to aid in identifying certain subpopulations who may be more at risk of adverse outcomes. Distinguishing these will play a key role in aggressive surveillance and management of patients with these risk factors to prevent mortality.

The following hypotheses will be tested:

FIRST HYPOTHESIS: H(0): For SPARCS NYS patients, there will be no change over time in the proportion of patients diagnosed with both a new thoracic aortic aneurysm (TAA) and a new bicuspid aortic valve (BAV) diagnoses *during the same index admission*.

SECOND HYPOTHESIS: H(0): For SPARCS NYS patients, there will be no change over time in the *proportion of patients with a newly diagnosed thoracic aortic aneurysm (TAA) after a pre-existing bicuspid aortic valve diagnosis*.

THIRD HYPOTHESIS H(0): For SPARCS NYS patients, there will be no change over time in the *proportion of patients with a newly diagnosed bicuspid aortic valve disease after a pre-existing thoracic aortic aneurysm diagnosis*.

Given this is research anticipated to advance the frontier of knowledge in this field, ad hoc exploratory analyses may be required to provide details to explain these hypothesis-based findings and/or to identify additional topics warranting future research (i.e., generate pilot data to initiate a new research project).

RESEARCH DESIGN AND METHODS:

This retrospective observational cohort study will be done using the SPARCS database. With the help of the SBU SOM Bioinformatics Department, the SPARCS database will be matched/merged to the enclosed coding listings to create a study-specific de-identified BAV/TAA patient database. Furthermore, the Bioinformatics team will be responsible for providing the descriptive statistics listed above as well as providing a study-database for future analyses. Bias will be assessed objectively with the Newcastle Ottawa Criteria for cohort studies.

SPARCS DATABASE ANALYSIS:

Using the SPARCS database (i.e. IRB approval previously received by Dr. Allison J. McLarty), a retrospective observational cohort study will be performed. Using the SPARCS Health Facts dataset, multivariable regression analysis using NYS records in the SPARCS dataset ranging from 2007-2018 will be performed.

With the assistance of the SBU SOM Bioinformatics Department and Biostatistics Core Lab, the SPARCS database will be matched and merged to the enclosed coding listings to create a study-specific de-identified BAV/TAA database. Bioinformatics and Biostatistics team members will be responsible for providing the descriptive statistics listed, as well as providing a study-database for future analyses. For the primary hypotheses of this study, which are related to BAV and TAA diagnoses in relation to each other over time, a p-value of 0.05 will be used. All

secondary and tertiary analyses, as well as additional exploratory analyses will use a p-value of <0.01. SAS version 9.4 will be used to complete all necessary statistical analysis for this study.

References

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Sample Table: Baseline TAA/BAV Sub-groups (1, 2, and 3) Patient Characteristics, Interventions, and Outcomes

Variable	Level	Subgroup 1 (TAA/BAV combined on index admission)	Subgroup 2 Old BAV and New TAA	Subgroup 3 Old TAA and New BAV	P-Value
Primary Variables of Interest – Time Trend					
Year	2005				
	2006				
	2007				
	2008				
	2009				
	2010				
	2011				
	2012				
	2013				
	2014				
	2015				
	2016				
	2017				
	2018				
p-value					
Time Periods					
Pre-February 2010					
March 2010 – December 2013					
January 2014-June 2015					
July 2015-					
p-value					
SES Special Interest Variables					
Gender	Female				
	Male				
Age continuous					
Age by deciles					
Age	<80				

	>80				
Race	White				
	Black				
	Native American or Alaskan Native				
	Asian				
	Native Hawaiian or other Pacific Islander				
	Other				
	Unknown				
Insurance	Commercial				
	Government				
	Other				
	No Insurance				
	Unknown				
Ethnicity	Hispanic				
	Non-Hispanic				
	Unknown				
Status	Elective				
	Urgent/Emergent				
Clinical Risk Factors					
Atherosclerotic Disease of Aorta	Yes				
Carotid Disease	Yes				
Coronary Artery Disease	Yes				
Congestive Heart Failure	Yes				
Hypertension:	Yes				
History of Myocardial Infarction	Yes				
Arrhythmia	Yes				
Prior PCI	Yes				
Resuscitation	Yes				

Cardiogenic Shock	Yes				
Hypotension	Yes				
Chest Pain	Yes				
Chronic Obstructive Pulmonary Disease	Yes				
Tobacco/ Smoking	Yes				
Cerebrovascular Disease	Yes				
Peripheral Vascular Disease	Yes				
Dialysis	Yes				
Hyperlipidemia	Yes				
Diabetes	Yes				
Obesity	Yes				
Liver Dysfunction	Yes				
Immunosuppression	Yes				
Neurological Deficit (hemiplegia, paraplegia)	Yes				
Anemia of Deficiency, iron deficiency	Yes				
Collagen Vascular Disease	Yes				
Hypothyroidism	Yes				
Comorbidity Scores					
Charlson Score					
Elixhauser Score					
Primary Endpoints					
Any Bad Thing Happening					
TAA Type	Rupture				
	Dissection				
	Death				
	Urgent Surgery				
	Emergent Surgery				

	"Any Bad Thing Happening"				
	Paralysis				
	Pacemaker				
	Paravalvular Leak (3+)				
	Access Complications				
	Cardiac Arrest				
	Acute Kidney Injury				
	Acute Myocardial Infarctions				
	Major Bleeding				
	Unplanned Coronary Intervention (i.e., PCI or CABG)				

CODES AND SUPPLEMENTARY INFORMATION:

Sample Table: ICD9/10 diagnosis codes for TAA, BAV and Other

Disease	ICD10	ICD9
Thoracic Aortic Aneurysm (TAA)-non rupture	I71.2	441.2
TAA-ruptured	I71.1	441.1
TAA-dissection	I71.01	441.01
Bicuspid Aortic Valve Dx – congenital insufficiency of aortic valve	Q23.1	746.4
Bicuspid Aortic Valve Dx – congenital stenosis of aortic valve	Q23.0	746.3