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In-hospital Outcomes Following Left Atrial Appendage Closure

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Abstract

Left atrial appendage closure (LAAC) is a non-pharmacologic approach for stroke prevention in patients with atrial fibrillation. The impact of comorbidity burden on adverse outcomes following LAAC is very important for clinical decision making. Cohort-based observational study was conducted to evaluate the association of comorbidity burden with in-hospital complications. Of 3294 participants (mean age was 75.7±8.2 years), 60% were male and 86% whites. The majority of participants undergoing LAAC presented with a significant number of comorbid conditions. The occurrence of in-hospital major adverse events (MAE) was 4.6%. Women and patients exhibiting higher Charlson Comorbidity Index (adjusted odds ratio [aOR]: 1.14, 95% confidence interval [CI]: 1.05-1.23, P=0.001), Elixhauser Comorbidity Score (aOR: 1.04, 95% CI: 1.02-1.07, P=0.002) and CHA_2DS_2-VASc (aOR: 1.11, 95% CI: 1.00-1.24, P=0.05) scores were associated with increased risk of in-hospital MAE after LAAC. Preprocedural comorbidity assessment is of paramount importance for risk stratification and further management of patients undergoing LAAC.

Key words: atrial fibrillation, stroke, prevention, anticoagulation, bleeding, women, sex disparities, elderly, left atrial appendage closure.

Summary for Lay Audience

Atrial fibrillation (AF) is an irregular heartbeat and can lead to fatal consequences like blood clots to the brain causing stroke and other heart-related complications such as heart failure. It is an increasingly common disease in the general population and is estimated to affect approximately 33.5 million people worldwide. Similarly, having multiple chronic diseases is becoming more common as the elderly population increases. The left atrial appendage (LAA) is a very small cavity of the heart placed in the upper left cavity of the heart (the left atrium). Convincing evidence shows that the LAA is the major source of blood clots and more than 90% of strokes originate in the LAA. Left atrial appendage closure (LAAC) is a nonpharmacologic procedure which closes off the opening of LAA in order to prevent blood clotting (stroke) in patients with AF. Validated chronic diseases scoring systems permit the estimation of worse outcomes in a wide spectrum of patients.

Cohort-based observational study was conducted to evaluate the association of comorbidity burden with in-hospital adverse outcomes. The results of this study including 3294 patients with AF who underwent LAAC showed that the majority of participants presented with a significant number of comorbid conditions, with more than half of the patients had ≥10 comorbidities. The occurrence of in-hospital major adverse events (MAE), including major bleeding, cardiovascular complications, vascular complications, cerebrovascular accident and acute kidney injury was 4.6%. Women and patients exhibiting a higher Charlson Comorbidity Index (CCI), Elixhauser Comorbidity Score (ECS) and CHA_2DS_2-VASc scores were independently associated with increased risk of in-hospital MAE after LAAC.

Our analysis also adds new data regarding the decrease in overall in-hospital MAE as compared to previous pre-FDA approval observational data. Moreover, we found that the pre-procedural CCI, ECS, CHA_2DS_2-VASc scores were associated with in-hospital MAE following LAAC.

Pre-procedural chronic diseases assessment can be an essential tool in the area of cardiology for risk stratification and further management of patients undergoing LAAC. The results of this study can be used to inform health policy makers of the potential risks of multiple chronic diseases in patients undergoing LAAC.

Co-Authorship Statement

This master's thesis and three manuscripts, Shubrandu Sanjoy conducted all the analyses and wrote the thesis components with the regular guidance of primary supervisor Dr. Rodrigo Bagur and co-supervisor Dr. Yun-Hee Choi. Both supervisors were involved all aspects of work and provided continuous feedback to the progress of thesis. Dr. Luciano Sposato, member of thesis supervisory committee, gave constructive feedback and supported on clinical issues to enrich the thesis. All co-authors have critically revised, provided intellectual contributions and approved the final version of the manuscripts. Three manuscripts are currently under review.

Dedications

This work is dedicated to my elder sister Shilpi Sutradhar, who inspires me from my childhood for my excellent academic career.

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List of abbreviations and acronyms

AHRQ	Agency for Healthcare Research and Quality
AF	atrial fibrillation
AKI	acute kidney injury
AUC	area under the curve
CABG	coronary artery bypass graft
CCI	Charlson comorbidity index
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior stroke or transient ischemic attack
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior stroke or transient ischemic attack, age 65 to 74 years, vascular disease (including previous myocardial infarction) and female sex
CMS	Centers for Medicare & Medicaid Services
COPD	chronic obstructive pulmonary disease
CI	confidence interval
DRG	diagnosis-related group
ECS	Elixhauser comorbidity score
HFRS	Hospital Frailty Risk Score
HCUP	Healthcare Cost and Utilization Project
HIV	Human immunodeficiency viruses
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IQR	interquartile range
LAA	left atrial appendage
LAAC	left atrial appendage closure
LOS	length of stay
MAE	mean absolute error
NIS	National Inpatient Sample
PCI	percutaneous coronary intervention
RCTs	randomized-controlled trials
RMSE	root-mean-square error
SD	standard deviation
TIA	transient ischemic attack
OR	odds ratio
US	United State

Chapter 1

Thesis organization, introduction, comorbidities measures and Thesis objectives

1.1. Thesis organization

Chapter 1: This chapter consists of rationale for conducting each of the studies that is included in this thesis.

Chapter 2: This chapter evaluates the impact of comorbidity burden on in-hospital outcomes among individuals who underwent left atrial appendage closure. A version of chapter two is currently under review (Manuscript 1).

Chapter 3: This chapter evaluates the impact of sex differences on in-hospital outcomes and, estimates sex-specific prediction models of adverse outcomes following left atrial appendage closure. A version of chapter three is currently under review (Manuscript 2).

Chapter 4: This chapter aims to compare in-hospital outcomes in patients ≥80 years with younger patients, and to determine whether global measures of comorbidity burden and frailty assessment are associated with increased risk of adverse events after LAAC. A version of chapter four is currently under review (Manuscript 3).

Chapter 5: This chapter includes study limitations, conclusion and future research.

Appendices: This section consists of ICD-10 codes for CCI, ECS, HFRS and adverse events, data use agreement for the Nationwide Databases from the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality and Curriculum Vitae.

1.2. Introduction

1.2.1. Atrial fibrillation

Atrial Fibrillation (AF) is the most common heart arrhythmia and an increasingly prevalent condition around the world. It was estimated that about 33.5 million people are affected with AF in 2010 worldwide and in Canada alone, about 350,000 people live with the diagnosis of AF. While the prevalence of AF is approximately 1-2% in the general population, it is expected to increase by 250% in 2050.[1] Various epidemiologic studies have shown that AF is more common in men than women.[2-5] Moreover, with aging, the incidence and prevalence of AF are higher than in the general population.[6-8]

At the same time, the prevalence of multimorbidity (two or more chronic conditions) also continues to increase.[9, 10] Common comorbidities such as myocardial infarction, hypertension, stroke, heart failure, chronic kidney disease and diabetes are some of the chronic conditions associated with increased risk of AF.[8, 11] Therefore, any additional comorbidity poses a significantly higher risk to AF patients.[12] It is thus evident that AF patients with multimorbidity would require special attention during treatment.[13]

Cerebrovascular accidents (including stroke and transient ischemic attack[TIA]) are a common complication on patients with AF.[14, 15] Indeed, AF-related stroke is approximately 3- to 5- fold higher in such patients.[16] It has also been found that the risk of stroke increases with age, with an incidence of about 1.5% in patients between 50 and 59 years of age and as high as 23.5% in patients between 80-89 years of age.[16, 17] Apart from the increased risk of stroke, there are other conditions that AF has been associated with, for instance, increased risk of heart failure and mortality, and hence, overall higher healthcare expenditures.[18-20]

To prevent stroke, oral anticoagulation therapy is used either with vitamin K Antagonists (VKA) or new-oral anticoagulants.[21] However, patients respond differently and some present with contraindications such as bleeding. The left atrial appendage (LAA) is the source of thrombus in over 90% of AF-related strokes.[22] Hence, for the subset of patients presenting with contraindications to oral anticoagulation therapy, left atrial appendage closure (LAAC) has been found to be a safe catheter-based interventional treatment.

1.2.2. Indications, safety and efficacy of left atrial appendage closure

Percutaneous LAAC is aimed at closing off the LAA, thereby reducing the ability of thrombus (blood clot) formation and risk of thromboembolism and therefore, a non-pharmacologic approach for stroke prevention in AF patients. The WATCHMAN LAA occluder (Boston Scientific, Natick, MA) device has been evaluated its safety and efficacy in randomized-controlled trials (RCTs),[23] and is the only one approved for commercial use by the Food and Drug Administration (March 13th, 2015) in the United States (US) to reduce the risk of stroke in patients with AF in whom long-term anticoagulation therapy is considered either suboptimal or contraindicated. The PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial was an early trial comparing the WATCHMAN device to the use of warfarin among AF patients with increased risk of stroke.[24] This prospective randomized controlled trial confirmed non-inferiority of the WATCHMAN device compared to oral anticoagulation using warfarin, regarding a composite of stroke, systemic embolism, and cardiovascular death.[24] More recent evidence has suggested that the WATCHMAN device shows improved procedural safety, with reduced rates of complications, possibly attributed to a better understanding of the procedure itself and an operator learning curve effect.[17, 25] Most studies examining the impact of LAAC on

intermediate and long-term clinical outcomes have been non-randomized cohort studies, which demonstrated that the annualized stroke rates are favourable compared to the expected rates as predicted by the $CHADS_2$ or CHA_2DS_2-VASc scores.[17]

1.3. Comorbidity measures

Comorbidities are defined as the presence of two or more concurrent chronic health conditions in an individual and these chronic conditions can lead to adverse health outcomes over the course of life.[26] In U.S., about 140 million people present with at least one or more chronic comorbidities and in Canada, one in three had at least one chronic condition.[26, 27] The Charlson Comorbidity Index (CCI) and Elixhauser Comorbidity Score (ECS) are global measures of comorbidity burden that were developed and validated for estimating prognosis and adverse clinical outcomes in a broad spectrum of patients, including those undergoing coronary and valvular heart interventions.[28-35] The CHA_2DS_2-VASc score is a well-known validated tool to predict the risk of thromboembolic events in patients with AF.[36-38] The Hospital Frailty Risk Score (HFRS) has been shown a useful tool to examine the presence and degree of frailty in the elderly.[39, 40] Patients undergoing LAAC present a higher burden of comorbidity and frailty, both of which often couple and influence clinical outcomes.[34, 39-42]

1.3.1. Charlson Comorbidity Index

Comorbidities of patients can be categorized based on the ICD diagnosis codes through the Charlson comorbidity index (CCI).[28] Mary Charlson who first developed, in 1987, the Charlson Comorbidity Index (CCI)[28] as a weighted index with 19 medical conditions (based on medical record review) in order to predict 1-year morality. Later in 1992, Deyo et al.[30] modified the CCI to 17 categories for administrative database with specific ICD diagnosis codes. These diagnosis

codes can be found in hospital abstracts data. The sum total of the 17 conditions (on a scale of 0 to 29) is used to define the total CCI score. The 17 components of CCI are: chronic myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease (COPD), rheumatoid disease, peptic ulcer disease without bleeding, mild and moderate/severe liver disease, peripheral vascular disease, cerebrovascular disease, dementia, diabetes mellitus (uncomplicated and complicated), hemiplegia, renal disease, cancer (any malignancy, including leukemia and lymphoma), metastatic solid tumour and AIDS (Acquired Immune Deficiency Syndrome).[30] The total of all the weights gives a single comorbidity score; thus, the higher the value, the higher the burden of comorbidities.

1.3.2. Elixhauser comorbidity score

The Elixhauser comorbidity score (ECS) [43] comprises of 30 binary comorbidity measures. For the purpose of these analyses, a modification of the ECS into a point system (scale -19 to 89) was adopted from van Walraven et al.[29] The 30 components of ECS and their points are: congestive heart failure (7 points), cardiac arrhythmias (5 points), valvular disease (-1 point), pulmonary circulation disorders (4 points), peripheral vascular disorders (2 points), hypertension with and without complications (0 point), paralysis (7 points), other neurological disorders (6 points), chronic pulmonary disease (3 points), diabetes with and without complications (0 point), hypothyroidism (0 point), renal failure (5 points), liver disease (11 points), peptic ulcer disease excluding bleeding (0 point), AIDS (0 point), lymphoma (9 points), metastatic cancer (12 points), solid tumour without metastasis (4 points), rheumatoid arthritis/collagen vascular diseases (0 point), coagulopathy (3 points), obesity(-4 points), weight loss (6 points), fluid and electrolyte disorders (5 points), blood loss anemia (-2 points), deficiency anemia (-2 points), alcohol abuse (0 point), drug abuse (-7 points), psychoses (0 point) and depression (-3 points). Each of the

components weighting is summed across the 30 conditions to define the total ECS score; thus, higher values indicate increasing comorbid burden.

1.3.3. CHA_2DS_2-VASc score

The CHA_2DS_2-VASc score estimates thromboembolic risk in patients with AF according to the clinical profile (on a scale of 0 to 9).[37, 38] The points vary across some of medical conditions, age and sex. For instance, congestive heart failure has 1 point, while 2 points are given for age 75 and above. Other conditions include prior stroke or transient ischemic attack (TIA [2 points]), diabetes mellitus (1 point), age between 65 and 74 years (1 point), vascular disease (including previous myocardial infarction, 1 point) and 1 point for the female sex.[38] This score is a validated tool to predict the risk of stroke and systemic emboli in patients with non-valvular atrial fibrillation. [37, 44, 45] The CHA_2DS_2-VASc score was further categorized into three risk zones [46]; low risk (score 0), moderate risk (score 1) and high risk (score ≥2).

1.3.4. Hospital Frailty Risk Score

The Hospital Frailty Risk Score (HFRS) was developed based on an observational study on claims-based ICD-10-dignosis codes. This was validated among patients aged ≥75 years in the United Kingdom. A total of 109 ICD-10-CM codes were considered in calculating the HFRS for each patient. The codes comprised of the first three characters ICD-10 codes from an index hospitalization. The risk of frailty was categorized as low (HFRS <5), intermediate (HFRS 5-15) or high (HRFS >15).[39]

1.3.5. International Classification of Diseases (ICD)

World Health Organization (WHO) categorized the International Classification of Diseases (ICD), ICD-10 codes based on health-related problems in different body system considering signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or diseases.[47] The ICD tenth revision (ICD-10), includes two major types of codes; Clinical Modification (ICD-10-CM) for diagnosis codes of diseases and Procedural Coding System (ICD-10-PCS) for procedure codes. The ICD-10 code was implemented in the U.S. from October 1, 2015 with approximately 70,000 codes. We used those ICD-10 codes to gather information regarding comorbidity burden as well as adverse outcomes.

1.4. Data source: Overview of National Inpatient Sample database

The National Inpatient Sample (NIS) represents the largest general publicly available database in the United States. The NIS includes discharges from all hospitals participating in the Healthcare Cost and Utilisation Project (HCUP), funded by the Agency for Healthcare Research and Quality (AHRQ) and accounts for approximately 20% stratified sample of all discharges from US community hospitals.[48] Without considering the anticipated payers, the NIS contains information on all hospital stays.[49]

The NIS is collected from the State Inpatient Databases (SID) and is part of inpatient information that now contributes to HCUP. From 2012 onwards, systematic sample was begun which is considered more efficient and it is a self-weighted sample, similar to random sampling design. The following essential factors are considered in the sampling: census division, ownership, location, teaching status, number of beds, diagnosis-related group (DRG) for the hospital stay, and month of stay in hospital. Discharges are categorized by the re-identified number of the hospital in each stratum. Every year, Centers for Medicare & Medicaid Services (CMS) collects detailed

reports of all-player, inpatient cost and charge information from hospitals to construct Cost-to-Charge ratio (CCR).[49, 50]

For obtaining discharge weights, the total number of discharges was divided by sample hospital discharge considering stratum in NIS.[49] Currently, NIS data is available up to 2017. We used two major steps to prepare data for analysis, firstly, ICD-10 procedure code 02L73DK (occlusion of left atrial appendage, percutaneous approach) was used to identify individuals who have undergone LAAC as a primary procedure between October 2015 and December 2017. Secondly, comorbidity scores (CCI, ECS), CHA_2DS_2-VASc and HFRS and in-hospital adverse outcomes were gathered using ICD-10 diagnosis codes. The primary and secondary diagnoses/procedures were determined from patient's demographic attributes, hospital features, projected cost source, entre charges, discharge status, the period of stay, and comorbidity.

1.5. Outcomes measure

The main outcome of interest was the occurrence of post-procedural major adverse events (MAE) that included the composite of post-procedural bleeding complications, cardiovascular complications, vascular complications, stroke or TIA and acute kidney injury. Post-procedural in-hospital complications were identified using ICD-10-CM codes.

1.6. Thesis objectives

The main objective of the master's thesis work was to assess the impact of comorbidities on in-hospital adverse events after LAAC. Particularly, the specific aims were: 1) to evaluate the association of comorbidity burden with in-hospital complications after LAAC, 2) to evaluate the impact of sex differences on in-hospital outcomes and, estimate sex-specific prediction models of adverse outcomes following LAAC and 3) to compare in-hospital outcomes in patients ≥80 years

with younger patients (<80 years), and to determine whether global measures of comorbidity burden and frailty assessment are associated with increased risk of adverse events after LAAC.

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Chapter 2

Comorbidity Burden in Patients Undergoing Left Atrial Appendage Closure

2.1. Abstract

Background: Information on comorbidity burden of patients undergoing left atrial appendage closure (LAAC) is still scant. Estimating the risk of unfavorable outcomes in relationship with comorbidities is crucial for clinical decision making. We aimed to evaluate the association of comorbidity burden with in-hospital complications after LAAC.

Methods: Cohort-based observational study using the United States National Inpatient Sample database, October 1st, 2015 to December 31st, 2017. The main outcome of interest was the occurrence of in-hospital major adverse events (MAE) defined as the composite of bleeding complications, acute kidney injury, vascular complications, cardiac complications and post-procedural stroke. Comorbidity burden and thromboembolic risk were assessed by the Charlson comorbidity index (CCI), Elixhauser comorbidity score (ECS) and CHA_2DS_2-VASc score. MAE were identified using ICD-10-CM codes. The associations of comorbidity with in-hospital MAE were evaluated using logistic regression models.

Results: Of 3294 participants (mean age was 75.7±8.2 years), 60% were male and 86% whites. The overall composite rate of in-hospital MAE after LAAC was 4.6%. Female sex (adjusted odds ratio [aOR]: 1.40, confidence interval [CI]: 1.01-1.97), and those with higher CCI (aOR: 1.14, 95% CI: 1.05-1.23, P=0.001), ECS (aOR: 1.04, 95% CI: 1.02-1.07, P=0.002), and CHA_2DS_2-VASc score (aOR: 1.11, 95% CI: 1.00-1.24, P=0.05) were significantly associated with in-hospital MAE. Internal 3-fold cross-validation with 100 repetitions showed an acceptable discriminative power and good performance of the models (root-mean square error and Brier score of 0.211 and 0.045).

Conclusion: In this large cohort of LAAC patients, the majority of them had significant comorbidity burden. In-hospital MAE occurred in 4.6% and female sex and those with higher burden of comorbidities were at higher risk of in-hospital MAE after LAAC.

Key words: atrial fibrillation, stroke, prevention, anticoagulation, bleeding, left atrial appendage closure

2.2. Introduction

Atrial fibrillation (AF) is the most prominent heart arrhythmia worldwide,[1] and is associated with a 3- to 5-fold increased risk of stroke in non-anticoagulated patients.[2-4] Moreover, the risk of stroke significantly increases with age,[1-3] and AF-related strokes are often more severe in terms of disability, costs, and mortality.[2-4] The left atrial appendage (LAA) is the major source of thromboembolism in patients with non-valvular AF, and previous data showed that more than 90% of strokes originated in the LAA.[5 6] Oral anticoagulation therapy is a class I indication for stroke prevention, especially for patients considered at high thromboembolic risk.[3 7] However, a significant proportion of patients are considered not to be eligible or have contraindications to anticoagulation therapy due to bleeding complications or are under-prescribed or sub-therapeutic.[8-11]

Left atrial appendage closure (LAAC) is a non-pharmacologic approach for stroke prevention in AF patients. The WATCHMAN LAA occluder (Boston Scientific, Natick, MA) device has been evaluated its safety and efficacy in randomized-controlled trials, and is the only one approved for commercial use by the Food and Drug Administration (March 13th, 2015) in the United States (US) to reduce the risk of stroke in patients with AF in whom long-term anticoagulation therapy is considered either suboptimal or contraindicated.

Most of patients undergoing LAAC are at high risk of both, thromboembolic and hemorrhagic events. In addition, these patients often have multiple comorbid conditions. As such, estimating the risk of unfavorable in-hospital outcomes is crucial for medical decision making. Therefore, we aimed to evaluate the impact of comorbidity burden on in-hospital outcomes among individuals who underwent LAAC.

2.3. Methods

2.3.1. Data Source

Cohort-based observational study using the National Inpatient Sample (NIS) database. The NIS is the largest all-payer inpatient health care database in the US and was developed by the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS includes discharges from all hospitals participating in the HCUP, approximating a 20% stratified sample of all discharges from US community hospitals.

2.3.2. Study Population

Individuals who had undergone LAAC as a primary procedure between October 1st, 2015 to December 31st, 2017 were identified by using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) procedure code 02L73DK (occlusion of left atrial appendage, percutaneous approach). We excluded patients if LAAC was performed as secondary procedure, meaning that the LAAC occurred during the same admission for other reasons. Information on patient demographics was obtained from each hospital discharge including, among others, age, sex, race and median household income according to residential ZIP code.

2.3.3. Comorbidity and thromboembolic risk assessment

Comorbid conditions were identified and categorized using 3 scores based on the Charlson comorbidity index (CCI),[12] Elixhauser comorbidity score (ECS)[13] and CHA_2DS_2-VASc thromboembolic risk scores. The CCI consists of 17 components and each component has an associated weight. The CCI score is defined as the weighted sum across the 17 conditions (scale 0 to 29) (**Appendix A**). The ECS consists of 30 binary comorbidity measures, however, the

modification of the ECS into a point system[14] (scale -19 to 89) was adopted for this analysis (**Appendix B**). The CHA_2DS_2-VASc score estimates thromboembolic risk in patients with AF according to the clinical profile (scale 0 to 9).[15] It includes congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 point), diabetes mellitus (1 point), prior stroke or transient ischemic attack (TIA [2 points]), age 65 to 74 years (1 point), vascular disease (including previous myocardial infarction, 1 point) and female sex (1 point).[16]

Each discharge record had information on up to 40 diagnoses that were used to identify each of the comorbidities required to determine the above three scores at the time of hospitalization.

2.3.4. Outcome measures

The main outcome of interest was the occurrence of in-hospital major adverse events (MAE) defined as the composite of bleeding complications, acute kidney injury, vascular complications, cardiac complications and post-procedural stroke. To account for post-procedural complications, MAE were identified using ICD-10-CM codes (**Appendix D**).

2.3.5. Statistical analysis

According to HCUP data use agreement, variables with <10 counts for individual discharge records are not detailed. Whenever missing data were >10% of the covariate data, the discharges with missing data were removed, assuming data was missing at random. Frequency of LAAC procedures and in-hospital MAE rates were divided quarterly considering three-month periods (January-March, April-June, July-September and October-December) on a calendar year.

In-hospital MAE was considered as binary outcome. Length of stay was computed by subtracting the admission date from the discharge date, as such, more than 85% of the patients had

1-day of hospital stay. Hospital volumes were determined based on the annual number of LAAC performed by each hospital in a given year.

Qualitative variables were expressed as number and percentages and quantitative variables as mean ± standard deviation or median (inter-quartile range [IQR]) depending on variable distribution. Comparison of continuous variables was performed using the two-sided Student's t test or Wilcoxon rank-sum test for means and medians, respectively, and the chi-square tests were used to compare categorical variables. Adjusted P-values for each variable were computed adjusting for survey sampling design by discharge-level weights, cluster (individual hospital) and strata provided by NIS and recommended by AHRQ during survey-specific analysis.[17] To identify factors associated with the main outcome, we first conducted the bivariate analysis for each outcome with single variable. Then, the variables associated with outcome variable from bivariate analysis with a P-value of <0.10 were included in multivariable models along with each scoring system (CCI, ECS and CHA_2DS_2-VASc scores).

Because patients in the NIS data were nested within hospitals (two-level hierarchical structure), in order to account for intra-cluster correlation within hospitals, multilevel modeling was performed allowing the intercepts to vary across hospitals. The variances of the random-effect were all close to zero after fitting multilevel logistic regression models for in-hospital complications (main outcome), therefore, the association between the CCI, ECS and CHA_2DS_2-VASc scores and in-hospital complications was examined with multivariable logistic regression models fitted separately for each scoring system.

For in-hospital MAE, each of the multivariable adjustments included age, sex, race and the CCI, ECS and CHA_2DS_2-VASc-score for Models 1 to 3, respectively. Age and sex are the components of CHA_2DS_2-VASc-score; hence, these were not included for adjustment in Model 3.

Area under the receiver operating characteristic curve (AUC) analysis was conducted for each model to assess its discrimination ability for in-hospital complications. Internal validation was conducted using 3-fold cross-validation to assess the prediction ability of each model on new data, and we followed an algorithm of 100 times 3-fold cross-validation.[18 19] As data was hierarchically structured, hospitals were divided into 3 folds, using stratified random sampling[18] which ensured equal participation of each hospital for both training part and testing part. In addition, to further assess each model's performance, the root-mean-square error (RMSE), mean absolute error (MAE) and Brier scores were calculated. The RMSE $=\sqrt{\sum_{i=1}^{n}(f_i - O_i)^2/n}$ measures the average prediction error, where f_i represents the predicted probability and O_i the observed outcome. The MAE = $\sum_{i=1}^{n}|f_i - O_i|/n$ measures the mean absolute prediction error for each model. The Brier score = $\sum_{i=1}^{n}(f_i - O_i)^2/n$ was calculated from mean squared error of prediction for each model. Statistically significant differences were considered at P-values of <0.05. All statistical analyses were performed by using statistical software R version 3.6.1.

2.4. Results

2.4.1. Study population

A total of 3294 participants who underwent LAAC as primary procedure, among these, 114 (3.5%) LAACs were performed in 2015 (October-December), 1017 (30.8%) in 2016 (January-December), while 2163 (65.7%) LAACs were performed in 2017 (January-December), **Table 2.1**. The mean number of LAAC performed annually at individual hospitals was 5.5 (ranged from 1 to 45), and about 44% of hospitals performed between 2 to 5 procedures and 24% between 6 to 10 procedures. (**Figure 2.1**).

The mean age of the study population was 75.7±8.2 years, 60% were male and 86% whites. The comorbidity distribution as defined by the CCI and ECS are presented in **Figures 2.2** and **2.3**, respectively. The mean $CHADS_2$ and CHA_2DS_2-VASc score were 2.7±1.3 and 4.3±1.5, respectively, and 98% of the patients were at high-risk of thromboembolism (CHA_2DS_2-VASc score ≥2), **Table 2.1**. The most prevalent components of the CHA_2DS_2-VASc score were hypertension (84.9%), age ≥75 years (59.4%), females (39.9%) and congestive heart failure (37.5%), **Figure 2.4**. Notably, 29.5% of the patients had previous stroke or TIA. The mean number of comorbidities was 12.3±5.3, and the mean CCI and ECS were 2.2±1.9 and 9.7±5.8, respectively. The remaining baseline characteristics of the population are presented in **Table 2.1**. The overall median LOS was 1 (IQR 1-1) day and median hospital cost was $24,143 (IQR $18,540-$30,232) USD, **Table 2.1**.

2.4.2. In-hospital MAE following LAAC

In-hospital post-procedural MAE occurred in 153 (4.6%) patients, namely, major bleeding (0.6%), cardiac complications (1.7%), vascular complications (0.5%), stroke/TIA (0.4%) and acute kidney injury (2.2%). Overall death was low and occurred in 0.2% of cases. Patients who experienced in-hospital MAE had more previous history of congestive heart failure (50% versus 37%, P=0.001), peripheral vascular disease (18% versus 10%, P=0.01), renal disease (33% versus 21%, P=0.001), dementia (5.9% versus 2.5%, P=0.01), coagulopathy (10% versus 3.6%, P<0.001) and anemia (32% versus 15%, P<0.001), **Table 2.1**.

A quarterly analysis shows that LAAC procedures increased gradually over time, from 114 cases between October and December 2015, to 357 cases between October and December 2016, and 666 cases between October and December 2017, **Figure 2.5**.

The proportion of patients with in-hospital MAE increased with comorbidity burden. The mean number of comorbidities as well as the mean CCI and ECS were significantly higher among those who experience MAE as compared to those who did not experience MAE (16.5±6.4 versus 12.1±5.1, P<0.001; 2.7±2.0 versus 2.2±1.9, P=0.004 and 11.2±5.9 versus 9.7±5.8, P=0.002, respectively), **Table 2.1**. The crude event rates for in-hospital MAE stratified by scoring systems are detailed in **Tables 2.2** and **2.3**.

2.4.3. Factors associated with in-hospital MAE

After adjusting for age, sex and race, female sex (aOR: 1.40, 95% CI: 1.01-1.97), and those with higher CCI (aOR: 1.14, 95% CI: 1.05-1.23, P=0.001), ECS (aOR: 1.04, 95% CI: 1.02-1.07, P=0.002), and CHA_2DS_2-VASc score (aOR: 1.11, 95% CI: 1.00-1.24, P=0.05) were significantly associated with in-hospital MAE, **Figure 2.6**.

The AUC for models 1, 2 and 3 were 0.59, 0.61 and 0.55, respectively. After 3-fold cross-validation with 100 repetitions, the average AUC, RMSE, MAE and Brier score were 0.57, 0.211, 0.089 and 0.045, respectively, for model 1; 0.58, 0.211, 0.089 and 0.045, respectively, for model 2; 0.53, 0.211, 0.089 and 0.045, respectively, for model 3 (**Figure 2.6**). Lower (close to 0) values of RSME, MAE and Brier score, indicate better fit of the model.

2.4.4. Length of hospital stay

The median LOS of the study population was 1 day, 2805 (85%) patients stayed ≤1 day and 489 (15%) patients >1 day. A greater proportion of patients who experienced MAE stayed >1 day compared to those who did not (72% versus 12%, P<0.001), **Table 2.1**.

2.5. Discussion

In this large cohort-based observational study including 3294 patients who underwent LAAC, we found that the number of procedures has notably increased from October 2015 to December 2017. The majority of participants presented with a significant number of comorbid conditions, with more than half of the patients had ≥10 comorbidities. The occurrence of in-hospital MAE, including major bleeding, acute kidney injury, vascular complications, cardiovascular complications and post-procedural stroke/TIA was 4.6%. Female sex and those exhibiting higher CCI, ECS, CHA_2DS_2-VASc scores were independently associated with increased risk of in-hospital MAE after LAAC.

2.5.1. In-hospital outcomes

In the present analysis, rates of major bleeding were lower (0.6%) with the reported (3.5%) in the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial,[8] tough comparable (0.4%) with the PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial.[9] Notably, the incidence of post-procedural stroke/TIA (0.4%) compares favorably with regards to PROTECT-AF[8] and is in line with PREVAIL[9] and more recent studies as well as using a different LAAC device.[10 11]

Between the first and the last analyzed quarter, we observed an increase in the number of cases by ≈6-fold, clearly matching the early national learning curve in LAAC. Therefore, the reported rate of in-hospital MAE may accurately reflect the current observed rates. Importantly, the present study shows a decrease in overall in-hospital MAE as compared to a previous pre-FDA

approval observational data, where, for instance, post-procedural stroke/TIA and death were reported in 3.3% and 2.3%, respectively.[20]

2.5.2. Association of comorbidities and adverse events

The CCI and ECS scores are global measures of comorbidity burden that were developed and validated for estimating prognosis and adverse clinical outcomes in a broad spectrum of patients, including those undergoing coronary and valvular heart interventions.[12 14 21-25] Interestingly, data suggest that the ECS may outperform the CCI in certain scenarios.[25 26] Our results indicate that comorbidity burden as assessed by the CCI was significantly associated with in-hospital MAE, and this finding is in line with observational pre-FDA approval data.[20] Noteworthy, that report showed a mean CCI of 0.98±1.13,[20] while ours shows a mean CCI of 2.2±1.9 and 56% of patients with a CCI ≥2, highlighting, therefore, a higher prevalence of comorbidities in this all-comer contemporaneous population. Moreover, our multivariable analysis shows an increased risk in in-hospital MAE per-unit increase in ECS, and this finding is relevant since little is known about the predictive value of the ECS in the setting of LAAC.

The CHA_2DS_2-VASc score is a well-known validated tool to predict the risk of thromboembolic events in patients with AF.[16] Furthermore, it has also been shown that this score may be useful to predict outcome in different clinical settings such as following acute coronary syndrome, cardiac surgery and transcatheter aortic valve implantation.[27-30] In our study, the mean $CHADS_2$ and CHA_2DS_2-VASc score were 2.7±1.3 and 4.3±1.5, and this is in line with the reported in randomized studies and slightly lower than registry data (2.8 and 4.5, respectively).[10 11] Conversely to the findings of the EWOLUTION[11] (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure

Technology) registry, where the incidence of serious adverse events at 7 and 30 days after LAAC did not appear to be influenced by a significant interaction of $CHADS_2$ <3/≥3 or CHA_2DS_2-VASc <5/≥5 scores, we found that the CHA_2DS_2-VASc score was strongly associated with in-hospital MAE following LAAC.

2.6. Limitations of the study

Our study has several limitations. The main limitation of this study lies in its observational nature. Second, because of an administrative database, coding errors may have occurred during data gathering. Indeed, as above stated, the outcomes of interest were identified using ICD-10-CM codes (**Appendix D**), therefore, specific details and adjudication (i.e. severity/degree of bleedings) may not have been accurately tracked. Also, there is a lack of granularity of certain variables that precluded the calculation of pre-procedural bleeding risk (i.e. HAS-BLED score). Hence, the effect modification of unmeasured variables should be considered when interpreting these results. Third, there is a lack of data regarding medications and concomitant periprocedural anticoagulation therapy, which might have had an impact on reported outcomes such as bleeding or cerebrovascular accidents. The interruption of oral anticoagulation has been associated as predictor of embolic events; hence, the inclusion of anticoagulation status would have added important information in terms of bleeding and ischemic/embolic complications beyond the inherent to the procedure. Furthermore, post-interventional and discharge medication (i.e. oral anticoagulants with or without concomitant antiplatelets) management was not available. Finally, we have in-hospital outcome data only, thus, unable to provide the impact of comorbid conditions on long-term follow-up, such as disabling stroke.

2.7. Conclusions

The majority of patients who underwent LAAC had significant comorbidity burden. Female sex and those exhibiting a higher CCI, ECS, CHA_2DS_2-VASc scores were strongly associated with increased risk of in-hospital MAE after LAAC. We present a comprehensive study to appraise the impact of pre-procedural comorbidities and further assessment as outcomes prediction models in this particular population, therefore, adding important data for clinical decision making.

2.8. Acknowledgment

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2.9. Competing interests

Dr. Holmes is on the Advisory Board for Boston Scientific, unpaid. The remaining authors of the study have no conflicts of interest inherent to the content of this manuscript.

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Table 2.1: Baseline characteristics of the study population and stratified by the occurrence of in-hospital MAE

	In-hospital MAE				Univariate analysis	
	All n=3294	**Yes n=153**	**No n=3141**	**Adjusted P-value[#]**	**OR (95% CI)**	**P-value**
Mean age, years	75.7±8.2	76.1±8.1	75.6±8.2	0.53	1.01 (0.99-1.03)	0.53
Women	1313 (40)	73 (48)	1240 (39)	**0.04**	1.40 (1.01-1.94)	**0.04**
Race*						
White	2738 (86)	121 (81)	2617 (87)	0.06	Reference	0.06
Non-white	434 (14)	28 (19)	406 (13)		1.49 (0.96-2.25)	
Median ZIP income**						
0-25th percentile	642 (20)	27 (18)	615 (20)	0.88	Reference	
26-50th percentile	803 (25)	35 (24)	768 (25)		1.04 (0.62-1.75)	0.89
51-75th percentile	926 (28)	46 (32)	880 (28)		1.19 (0.74-1.96)	0.48
76-100th percentile	875 (27)	38 (26)	837 (27)		1.03 (0.63-1.73)	0.90
Comorbidities						
Smoking	1123 (34)	43 (28)	1080 (34)	0.11	0.75 (0.51-1.06)	0.11
Dyslipidemia	1931 (59)	95 (62)	1836 (58)	0.37	1.16 (0.84-1.63)	0.37
Hypertension	2796 (85)	129 (84)	2667 (85)	0.84	0.96 (0.62-1.53)	0.84
Diabetes mellitus	1092 (33)	55 (36)	1037 (33)	0.45	1.14 (0.81-1.59)	0.45
Previous myocardial infarction	390 (12)	23 (15)	367 (12)	0.21	1.34 (0.83-2.07)	0.21
Previous PCI	63 (1.9)	<10 (1.3)	61 (1.9)	0.57	0.67 (0.11-2.17)	0.58
Previous CABG	502 (15)	24 (16)	478 (15)	0.88	1.04 (0.65-1.59)	0.88
Congestive heart failure	1236 (38)	77 (50)	1159 (37)	**0.001**	1.73 (1.25-2.40)	**0.001**
Valvular disease	680 (21)	34 (22)	646 (21)	0.62	1.10 (0.74-1.61)	0.62
Previous cerebrovascular disease	972 (30)	35 (23)	937 (30)	0.07	0.70 (0.47-1.01)	0.07
Peripheral vascular disease	355 (11)	27 (18)	328 (10)	**0.01**	1.84 (1.17-2.78)	**0.01**
Chronic pulmonary disease	695 (21)	32 (21)	663 (21)	0.95	0.99 (0.65-1.45)	0.95
Renal disease	709 (22)	50 (33)	659 (21)	**0.001**	1.83 (1.28-2.58)	**0.001**
Obesity	495 (15)	27 (18)	468 (15)	0.35	1.22 (0.78-1.85)	0.35
Peptic ulcer disease	41 (1.2)	<10 (1.3)	39 (1.2)	0.94	1.05 (0.17-3.48)	0.94
Dementia	87 (2.6)	<10 (5.9)	78 (2.5)	**0.01**	2.45 (1.13-4.74)	**0.01**
Rheumatic disease	97 (2.9)	<10 (3.3)	92 (2.9)	0.81	1.12 (0.39-2.53)	0.81
Liver disease	87 (2.6)	<10 (0.7)	86 (2.7)	0.12	0.23 (0.01-1.06)	0.15
Hypothyroidism	542 (16)	29 (19)	513 (16)	0.39	1.20 (0.78-1.79)	0.39
Coagulopathy	129 (3.9)	16 (10)	113 (3.6)	**<0.001**	3.13 (1.74-5.28)	**<0.001**

Cancer	73 (2.2)	<10 (2.0)	70 (2.2)	0.83	0.88 (0.21-2.39)	0.83
Anemia	513 (16)	49 (32)	464 (15)	**<0.001**	2.72 (1.89-3.85)	**<0.001**
Depression	238 (7.2)	<10 (5.9)	229 (7.3)	0.51	0.79 (0.37-1.49)	0.51
$CHADS_2$ score	2.7±1.3	2.8±1.3	2.7±1.3	0.75	1.02 (0.90-1.16)	0.75
<2	522 (16)	25 (16)	497 (16)	0.86	Reference	
≥2	2772 (84)	128 (84)	2644 (84)		0.96 (0.63-1.53)	0.86
CHA_2DS_2-VASc score	4.3±1.5	4.5±1.6	4.3±1.5	0.09	1.11 (0.99-1.23)	0.06
<2	56 (1.7)	<10 (2.0)	53 (1.7)	0.80	Reference	
≥2	3238 (98)	150 (98)	3088 (98)		0.86 (0.31-3.55)	0.80
Number of comorbidities	12.3±5.3	16.5±6.4	12.1±5.1	**<0.001**	1.15 (1.12-1.18)	**<0.001**
Charlson comorbidity index	2.2±1.9	2.7±2.0	2.2±1.9	**0.004**	1.14 (1.05-1.23)	**0.002**
0	546 (17)	18 (12)	528 (17)	**0.04**	Reference	
1	895 (27)	35 (23)	860 (27)		1.19 (0.68-2.17)	0.55
2	670 (20)	29 (19)	641 (20)		1.33 (0.74-2.46)	0.35
≥3	1183 (36)	71 (46)	1112 (36)		1.87 (1.13-3.27)	**0.02**
Elixhauser comorbidity score	9.7±5.8	11.2±5.9	9.7±5.8	**0.002**	1.04 (1.02-1.07)	**0.002**
≤0	37 (1.1)	<10 (1.3)	35 (1.1)	**0.004**	Reference	
1-5	1189 (36)	34 (22)	1155 (37)		0.52 (0.15-3.25)	0.38
6-10	672 (21)	36 (24)	636 (20)		0.99 (0.29-6.25)	0.99
≥11	1396 (43)	81 (53)	1315 (42)		1.08 (0.32-6.71)	0.92
Year of procedure						
2015 (October-December)	114 (3.5)	10 (6.5)	104 (3.3)	0.11	Reference	
2016 (January-December)	1017 (31)	45 (29)	972 (31)		0.48 (0.24-1.04)	0.04
2017 (January-December)	2163 (66)	98 (64)	2065 (66)		0.49 (0.26-1.03)	0.04
Length of stay, days	1 (1-1)	3 (1-6)	1 (1-1)	**<0.001**	1.58 (1.47-1.70)	**<0.001**
≤1 day	2805 (85)	43 (28)	2762 (88)	**<0.001**	Reference	**<0.001**
>1 day	489 (15)	110 (72)	379 (12)		18.64 (13.00-27.20)	
Index admission cost, USD[§]	24,143 (18,540-30,232)	33,014 (24,394-38,966)	23,914 (18,417-29,833)	**<0.001**	1.01 (1.00-1.01)	**<0.001**

Values are expressed as mean ± standard deviation, median (interquartile range) or counts (%) unless otherwise noted. Exact counts for variables with <10 patients are not detailed as per the Healthcare Cost and Utilization Project data use agreement. MAE: major adverse events. [#]Adjusted P-values for each variable were computed from adjusting sampling design by discharge-level weights, cluster and strata. OR: odd ratio. CI: confidence interval. *Race was missing in 3.7% **Median ZIP income was missing in 1.6%. [§]Total cost was missing 0.3%, CABG: coronary artery bypass surgery. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack, Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category. USD: United States dollar.

Table 2.2: Distribution of in-hospital major adverse events (MAE) stratified by comorbidity scoring systems

	Overall MAE* n=153	Bleeding complications n=19	Acute kidney injury n=74	Cardiac complications n=55	Vascular complications n=16	Post-procedural stroke/TIA n=14
Charlson Comorbidity Index						
0, n=546	11.8%	21.1%	5.4%	16.4%	25.0%	21.4%
1, n=895	22.8%	5.3%	13.5%	36.4%	18.8%	21.4%
2, n=670	19.0%	21.1%	18.9%	21.8%	18.8%	0%
≥3, n=1183	46.4%	52.6%	62.2%	25.4%	37.4%	57.1%
Elixhauser Comorbidity Score						
≤0, n=37	1.3%	0%	0%	1.8%	0%	7.1%
1 to 5, n=1189	22.2%	26.3%	8.1%	30.9%	37.5%	42.9%
6 to 10, n=672	23.5%	31.6%	24.3%	27.3%	12.5%	7.1%
≥11, n=1396	53.0%	42.1%	67.6%	40.0%	50.0%	42.9%
CHA_2DS_2-VASc Score						
0 (Low), n=4	0.7%	0%	0%	0%	0%	7.1%
1 (Intermediate), n=52	1.3%	0%	2.7%	1.8%	0%	0%
≥2 (High), n=3238	98.0%	100%	97.3%	98.2%	100%	92.9%

Values are expressed as %. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack (TIA), Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category. *Numbers do not add up due to some patients having had more than 1 complication. Death rate was 0.2%.

Table 2.3: Average scoring systems stratified by in-hospital major adverse events (MAE)

Major adverse events		Charlson Comorbidity Index	Elixhauser Comorbidity Score	CHA_2DS_2-VASc Score
Overall in-hospital MAE	Yes	2.7	11.2	4.5
	No	2.2	9.7	4.3
	P-value	**0.002**	**0.002**	0.06
Bleeding complications	Yes	2.6	9.9	4.7
	No	2.2	9.7	4.3
	P-value	0.41	0.90	0.22
Acute kidney injury	Yes	3.2	13.1	4.4
	No	2.2	9.7	4.3
	P-value	**<0.001**	**<0.001**	0.51
Cardiac complications	Yes	2.1	9.5	4.3
	No	2.2	9.7	4.2
	P-value	0.54	0.78	0.90
Vascular complications	Yes	2.5	10.0	4.3
	No	2.2	9.7	4.2
	P-value	0.56	0.85	0.90
Stroke/TIA	Yes	3.2	10.6	5.1
	No	2.2	9.7	4.3
	P-value	**0.05**	0.59	**0.04**

CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack (TIA), Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category. MAE: major adverse events

Figure 2.1: Left atrial appendage closure (LAAC) annual volumes among individual hospitals between October 2015 and December 2017.

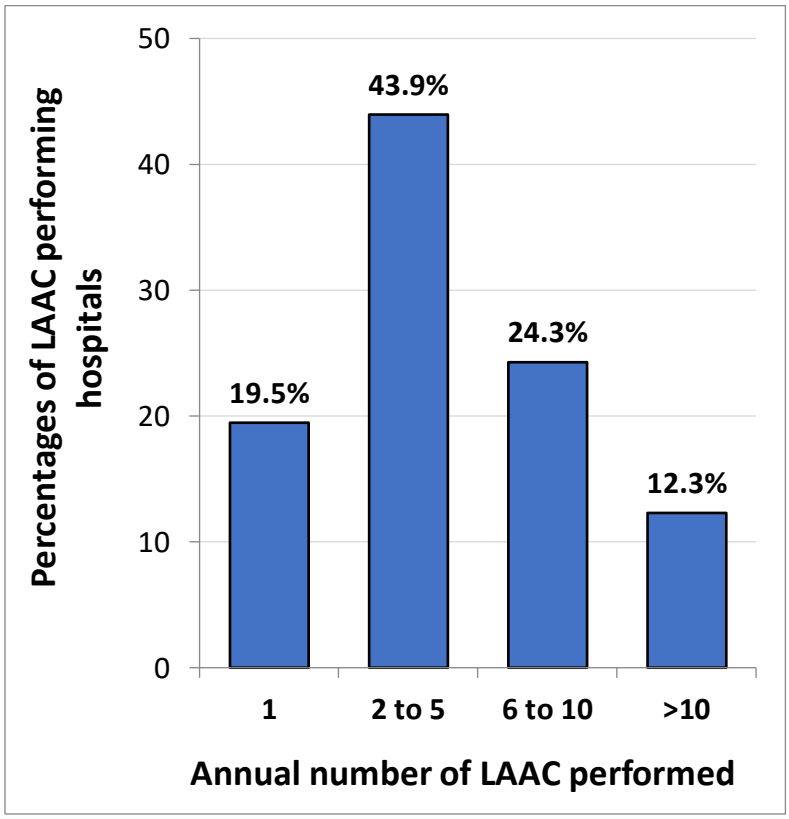
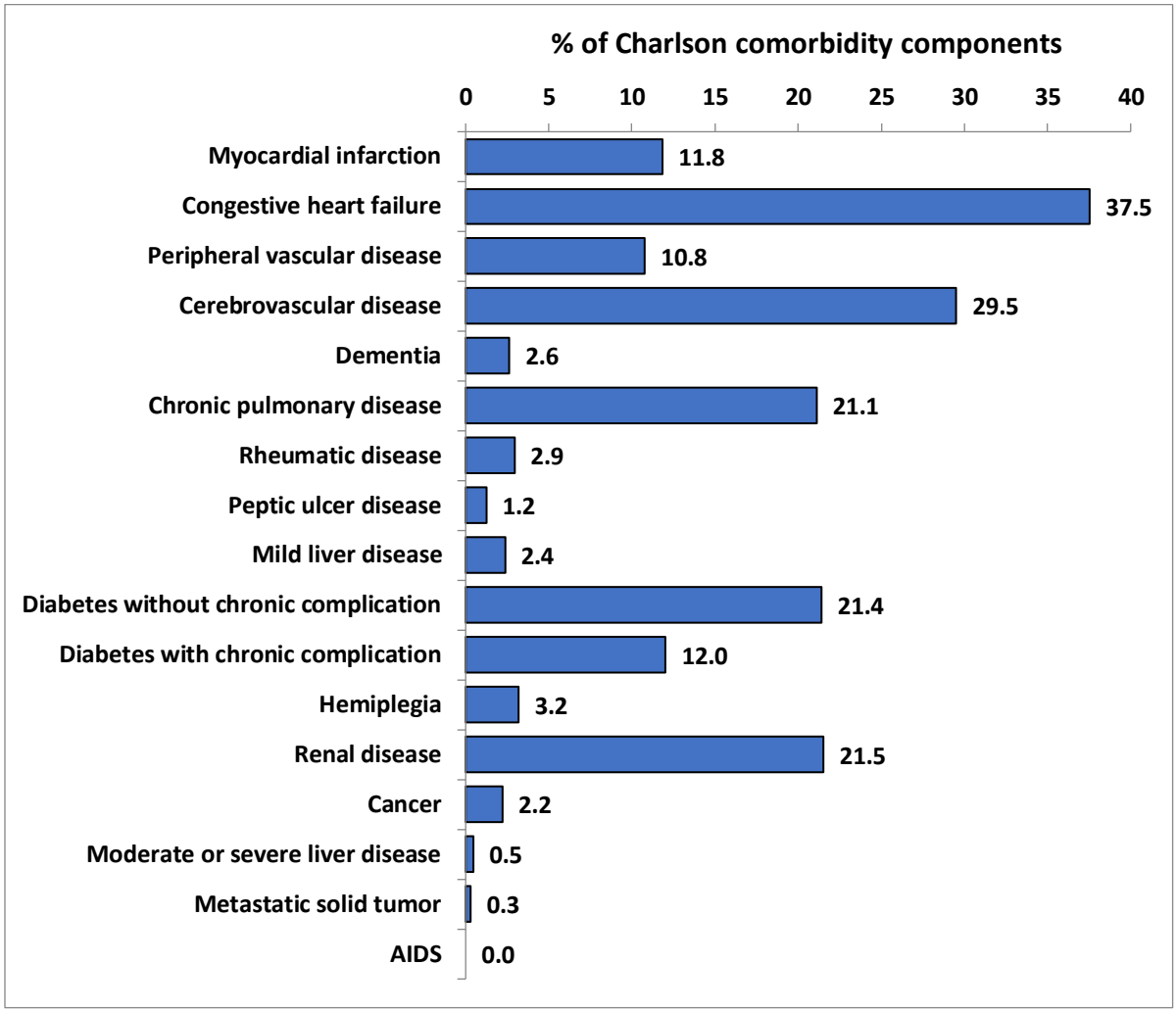
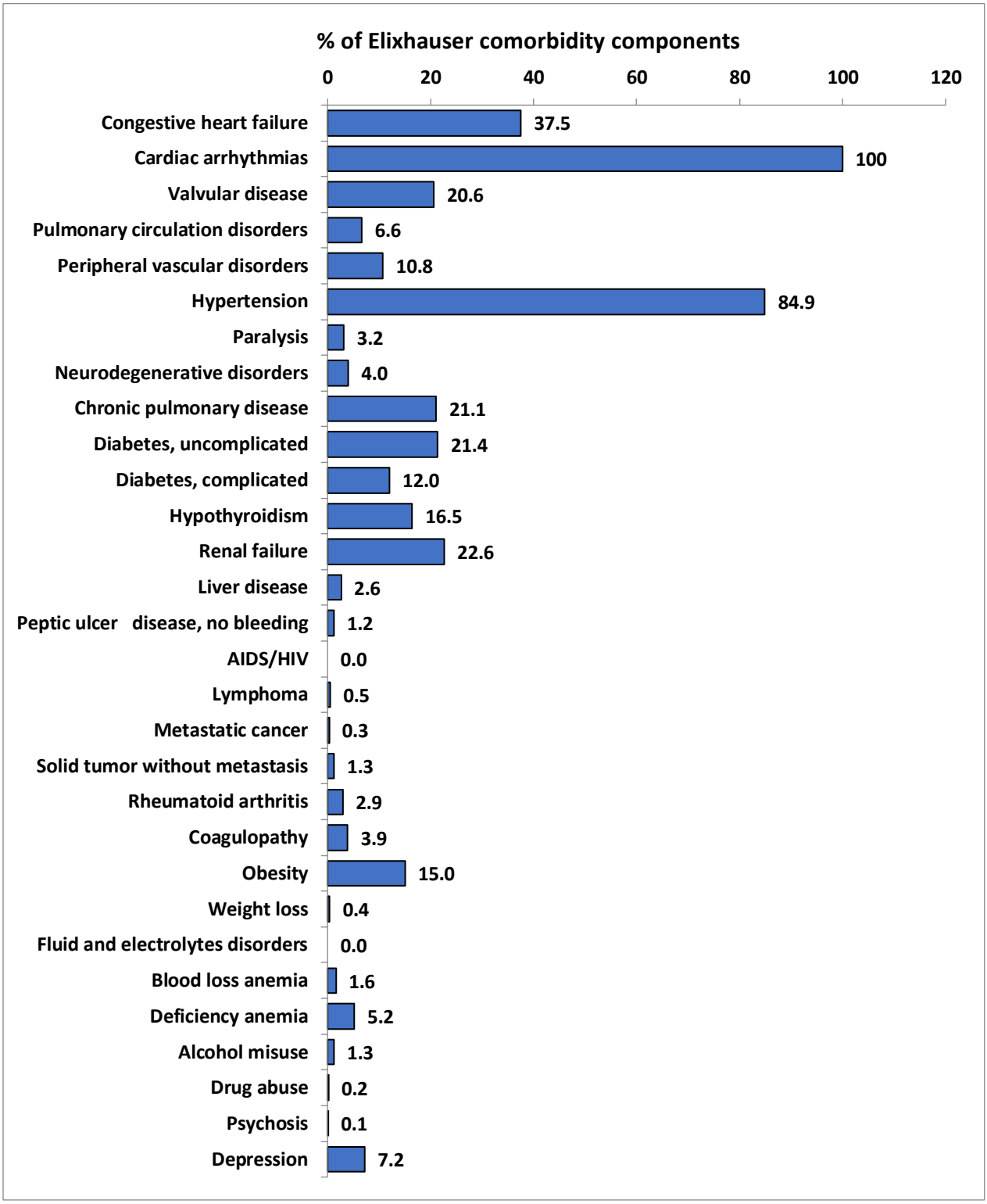


Figure 2.2: Proportion of components in Charlson Comorbidity Index.



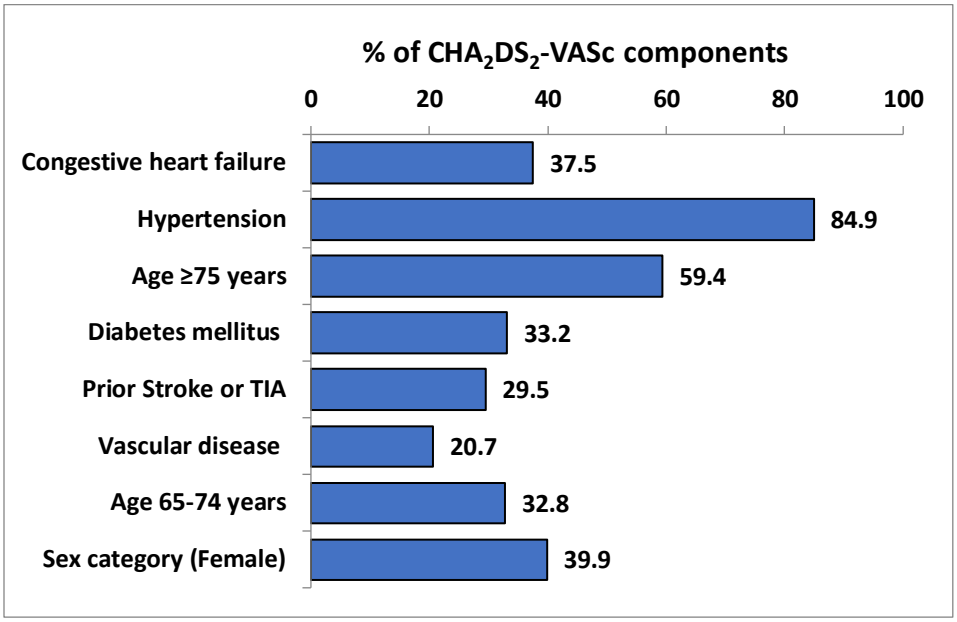
AIDS: acquired immune deficiency syndrome.

Figure 2.3: Proportion of components in Elixhauser Comorbidity Score



AIDS/HIV: acquired immune deficiency syndrome and human immunodeficiency virus infection.

Figure 2.4: Proportion of components in CHA_2DS_2-VASc score.



CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack, Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category.

Figure 2.5: Temporal trends in left atrial appendage closure (LACC) procedures performed quarterly and in-hospital major adverse events from 2015-2017.

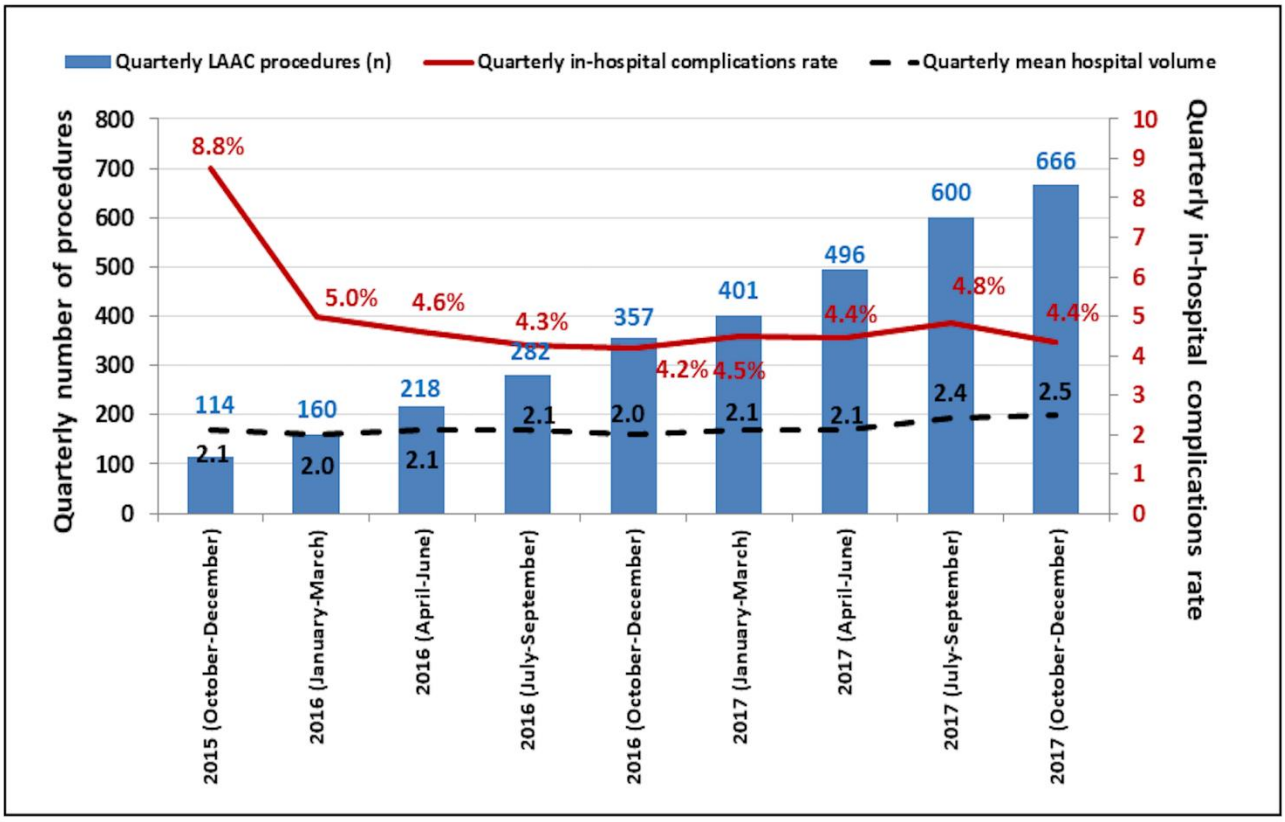
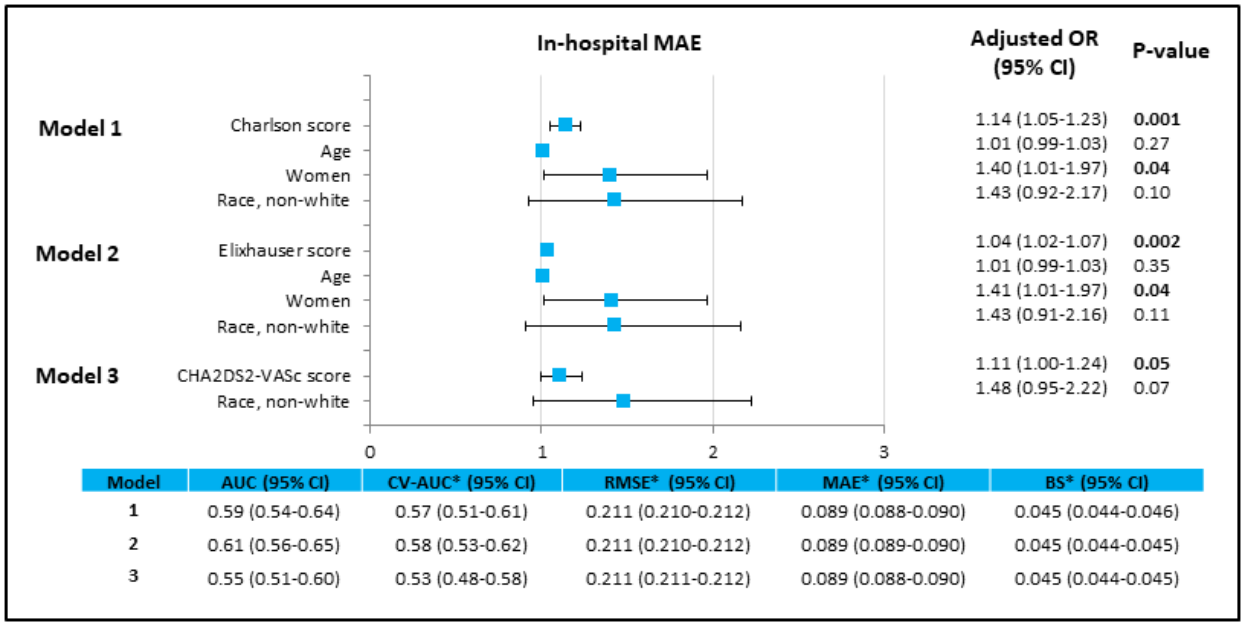


Figure 2.6: Multivariable logistic regression analyses for any in-hospital major adverse events (MAE).



Model	AUC (95% CI)	CV-AUC* (95% CI)	RMSE* (95% CI)	MAE* (95% CI)	BS* (95% CI)
1	0.59 (0.54-0.64)	0.57 (0.51-0.61)	0.211 (0.210-0.212)	0.089 (0.088-0.090)	0.045 (0.044-0.046)
2	0.61 (0.56-0.65)	0.58 (0.53-0.62)	0.211 (0.210-0.212)	0.089 (0.089-0.090)	0.045 (0.044-0.045)
3	0.55 (0.51-0.60)	0.53 (0.48-0.58)	0.211 (0.211-0.212)	0.089 (0.088-0.090)	0.045 (0.044-0.045)

CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack, Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category. OR: odds ratio. CI: confidence interval. Models 1, 2 and 3 were adjusted by age, sex, race, and Charlson-weighted score, age, sex, race and Elixhauser-weighted score and race and CHA_2DS_2-VASc score, respectively. OR for continuous variables are presented as per-unit increase. AUC: Area under the curve. CV: Cross Validation. RMSE: Root Mean Squared Error. MAE: Mean Absolute Error: BS: Brier score. CV-AUC*, RSME*, MAE*, and BS* were computed through 3-fold cross validation with 100 repetitions. Lower (close to 0) values of RSME, MAE and Brier score, indicate better fit of the model. Blue squares with whiskers denote the OR and its CI of in-hospital MAE.

Chapter 3

Sex Differences in Outcomes Following Left Atrial Appendage Closure

3.1. Abstract

Background: Information on sex-related differences and clinical outcomes following left atrial appendage closure (LAAC) is still scant. We aimed to evaluate the impact of sex on in-hospital outcomes and, to estimate sex-specific prediction models of adverse outcomes following LAAC.

Methods: Cohort-based observational study querying the National Inpatient Sample database between October 2015 to December 2017. Demographics, baseline characteristics, and comorbidities were assessed by the Charlson comorbidity index (CCI), Elixhauser comorbidity score (ECS) and CHA_2DS_2-VASc score. The primary outcome was in-hospital major adverse events (MAE) defined as the composite of bleeding, vascular, cardiac complications, post-procedural stroke and acute kidney injury. The associations of the CCI, ECS and CHA_2DS_2-VASc score with in-hospital MAE were examined using logistic regression models for women and men, respectively.

Results: A total of 3294 subjects were identified, of which, 1313 (40%) were women and 1981 (60%) men. Women were older (76.3±7.7 versus 75.2±8.4 years, P<0.001), had a higher CHA_2DS_2-VASc score (4.9±1.4 versus 3.9±1.4, P<0.001) but showed lower CCI and ECS compared with men (2.1±1.9 versus 2.3±1.9, P=0.01 and 9.3±5.9 versus 9.9±5.7, P=0.002, respectively). The primary composite outcome occurred in 4.6% of patients and was higher in women compared with men (women 5.6% versus men 4.0%, P=0.04), and this was mainly driven by the occurrence of cardiac complications (2.4% versus 1.2%, P=0.01). Increase in CCI (adjusted odds ratio [aOR]): 1.24, 95% confidence interval [CI]: 1.11-1.38, P<0.001), ECS (aOR 1.05, 95% CI: 1.01-1.09, P=0.02) and CHA_2DS_2-VASc score (aOR: 1.26, 95% CI: 1.07-1.50, P=0.004) were associated with

increased risk of in-hospital MAE in women. Non-whites and per-unit increase in ECS (aOR: 1.04, 95% CI: 1.00-1.08, P=0.04) were associated with increased risk of in-hospital MAE in men. After 3-fold cross-validation with 100 repetitions, we found an acceptable discriminative power and performance of the models.

Conclusions: Women had higher rates of in-hospital complications following LAAC and burden of comorbidities was strongly associated with adverse outcomes. Further research is warranted to identify sex-specific pathways during patient's selection process to minimize complications in women undergoing LAAC.

Key words: women, sex disparities, atrial fibrillation, stroke, anticoagulation, bleeding, left atrial appendage closure

3.2. Introduction

Atrial fibrillation (AF) is the most prevalent heart arrhythmia worldwide and is associated with a 3- to 5-fold increased risk of stroke in non-anticoagulated patients.[1-4] Although men are at 1.5- to 2-fold higher risk of developing AF as compared to women, women who develop AF are at increased risk of stroke, cardiac events, all-cause and cardiovascular mortality compared with men.[5, 6] Female sex, therefore, is a variable included in cardioembolic risk scores for patients with non-valvular AF.[7, 8]

While the mainstay of stroke prevention for AF is oral anticoagulation therapy, these drugs are underused in women with AF.[9, 10] Moreover, studies have shown that women are at higher risk of either stroke or bleeding events than men when on oral anticoagulants,[11, 12]

Left atrial appendage closure (LAAC) is a non-pharmacologic treatment for thromboembolic prevention in patients with non-valvular AF and has been shown to be safe and efficacious compared to warfarin therapy in reducing the risk of stroke in patients when long term anticoagulation is considered suboptimal or contraindicated;[13] however, little is known about sex differences and clinical outcomes following LAAC. Therefore, we aimed to evaluate the impact of female sex on in-hospital outcomes and, to estimate sex-specific prediction models of adverse outcomes following LAAC.

3.3. Methods

3.3.1. Data Source

Cohort-based observational study using the National Inpatient Sample (NIS) database, a nationally representative and all-payer publicly available inpatient health care database in the United States. The NIS database was developed by the Healthcare Cost and Utilization Project (HCUP), created

by Agency for Healthcare Research and Quality (AHRQ) and contains approximately 20% stratified weighted sample of all discharges from United States community hospitals.[14]

3.3.2. Study Population

Individuals who underwent LAAC, as a primary procedure, between October 2015 and December 2017 were identified through the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) procedure code 02L73DK (occlusion of left atrial appendage with intraluminal device, percutaneous approach). The WATCHMAN LAA occluder (Boston Scientific, Natick, MA), is the only such device approved for commercial use in the United States. Data regarding patient's demographics including age, sex, race, admission type, median household income according to residential ZIP code, and comorbidities were gathered from each hospital discharge record through ICD-10-CM codes.

Comorbidity burden was identified using two validated comorbidity scoring systems, the Charlson comorbidity index (CCI)[15] and Elixhauser comorbidity score (ECS).[16] The CCI consists of 17 comorbidities and each of them has an associated weighting without age, which is summed across the 17 conditions to define the total CCI score (scale 0 to 29) (**Appendix A**). The ECS consists of 30 comorbidity measures and its modification into a point system[17] (scale -19 to 89) was adopted for this analysis (**Appendix B**). The CHA_2DS_2-VASc score was used to estimate the pre-procedural thromboembolic risk.[7, 8]

3.3.3. Outcome Measures

The primary outcome of interest of this study was the composite of in-hospital major adverse events (MAE) including post-procedural bleeding complications, cardiovascular complications, vascular

complications, stroke or transient ischemic attack (TIA) and acute kidney injury. In-hospital MAE were identified using ICD-10-CM codes and are detailed in **Appendix D**.

3.3.4. Statistical Analysis

Categorical variables are shown as counts and percentages and continuous variables are presented as mean ± standard deviation or median (inter-quartile range [IQR]) according to variable distribution. Differences between women and men were assessed using the chi-square test for categorical variables and the two-sided Student's t-test or Wilcoxon rank-sum test for continuous variables, accordingly, adjusting for a survey sampling design. Adjusted P-values for each variable were computed adjusting for sampling discharge-level weights, cluster and strata provided by NIS and recommended by AHRQ during survey-specific analysis.

According to HCUP data use agreement, the tabulated counts less than 10 for individual discharge records cannot be reported and hence, they were replaced with "<10" in tables. Frequency of LAAC procedures and in-hospital complications rates for women and men were divided quarterly into three-month periods (January-March, April-June, July-September and October-December) per calendar year.

The Cochran-Armitage trend test was used for detecting differences in trends for complications over the time. Length of stay was computed by subtracting the admission date from the discharge date. Hospital volumes were determined based on the annual number of LAAC performed by each hospital in a given year.

To identify factors associated with primary outcome, we first conducted the univariate analysis for each outcome with a single variable, then, the variables associated with outcome variable with a P-value of <0.10 were included in multivariable models along with each scoring system (CCI, ECS and CHA_2DS_2-VASc scores). To account for the two-level hierarchical structure

of NIS database (patients are nested within hospitals), multilevel modeling was applied allowing the intercepts to vary across hospitals. The variances of the random-effect were all close to zero after fitting multilevel logistic regression models for the primary outcome, therefore, multivariable logistic regression models were fitted separately for women and men to evaluate the association of the CCI, ECS and CHA_2DS_2-VASc scores with in-hospital MAE.

All models were fitted separately for women and men. Each of the multivariable models included age, race and the following: CCI-weighted score (Model 1); ECS-weighted score (Model 2); CHA_2DS_2-VASc-score (Model 3). Age was not included for adjustment in Model 3 because it is a component of the CHA_2DS_2-VASc-score.

Area under the receiver operating characteristic curve (AUC) analysis was conducted for each model to assess its discrimination ability for both in-hospital MAE. Internal validation was conducted using 3-fold cross-validation to assess the predictive ability of each model on new data, and we followed an algorithm of 100 times 3-fold cross-validation.[18, 19] To preserve the hierarchically structure of data, hospitals were spitted into 3 folds, using stratified random sampling[18] which ensured equal participation of each hospital for both training part and testing part. To further assess each model's performance, the Brier score was calculated from mean squared error of prediction for each model. Lower (close to 0) values of Brier score indicate better fit of the model. Statistically significant differences were considered at P-values of <0.05. Statistical analysis was performed using R version 3.6.1.[20]

3.4. Results

3.4.1. Study population

From October 2015 through December 2017, a total of 3294 patients were identified in the NIS as undergoing LAAC as a primary procedure. Of these, 1313 (40%) were women (85% white) and

1981 (60%) were men (87% white). Baseline characteristics according to sex are presented in **Table 3.1**. Women were older (76.3±7.7 years versus 75.2±8.4 years, P<0.001) but showed lower CCI and ECS compared with men (2.1±1.9 versus 2.3±1.9, P=0.01 and 9.3±5.9 versus 9.9±5.7, P=0.002), **Table 3.1**. The sex-based distribution of CCI and ECS are presented in **Figure 3.1** and **Figure 3.2**, respectively. As expected, women had higher CHA_2DS_2-VASc score (4.9±1.4 versus 3.9±1.4, P<0.001) and 99% of women and 97% of men presented a high (CHA_2DS_2-VASc score ≥2) thromboembolic risk (**Table 3.1**). The most prevalent components of the CHA_2DS_2-VASc score were hypertension, age ≥75 years, and congestive heart failure. Notably, 31.2% of women and 28.4% of men had previous stroke or TIA (**Figure 3.3**).

3.4.2. Sex-differences and clinical outcomes

The primary composite outcome occurred in 4.6% of patients, with significant difference between sexes (women 5.6% versus men 4.0%, P=0.04), mainly driven by cardiac complications (2.8% versus 1.2%, P=0.01). Overall death occurred in 0.2% without differences in sexes, **Table 3.1**.

A quarterly analysis shows that LAAC procedures gradually increased over time for both sexes (**Figure 3.4**). Notably, while in-hospital MAE significantly decreased from 13.9% in October-December 2015 to 5.8% in October-December 2017 among women (P_{trend}=0.03), it also decreased from 6.4% to 3.3% in men, but this was not statistically significant for men (P_{trend}=0.63).

Women who experienced in-hospital MAE were more likely to have a history of myocardial infarction, renal disease, congestive heart failure, peripheral vascular disease, dementia and anemia, whereas men were more likely to have a history of congestive heart failure, renal disease, coagulopathy and anemia, **Table 3.2**.

The proportion of in-hospital MAE increased with comorbidity burden in women. A higher CCI (3.0±2.2 versus 2.1±1.9, P=0.001) and higher ECS (11.0±6.2 versus 9.2±5.9, P=0.02) were

observed in women with in-hospital MAE, **Table 3.2**. Women who experienced in-hospital MAE presented with higher CHA_2DS_2-VASc scores (5.3±1.5 versus 4.8±1.4, P=0.01), **Table 3.2**. Men who experienced in-hospital MAE showed similar CCI (2.5±1.8 versus 2.3±1.8, P=0.42) and CHA_2DS_2-VASc score (3.7±1.4 versus 3.9±1.4, P=0.35) and higher ECS (11.4±5.6 versus 9.9±5.7, P=0.03) compared to counterparts who did not experience MAE, **Table 3.2**.

3.4.3. Factors associated with in-hospital MAE

After adjusting for age, race, Charlson-weighted score, Elixhauser-weighted score and CHA_2DS_2-VASc score, the risk of in-hospital MAE was higher among women per unit of increase in CCI (OR: 1.24, 95% CI: 1.11-1.38), ECS (OR: 1.05, 95% CI: 1.01-1.09) and CHA_2DS_2-VASc (OR: 1.26, 95% CI: 1.07-1.50) scores, **Figure 3.5**. In men, non-whites and per unit increase in ECS (OR: 1.04, 95% CI: 1.00-1.08) were associated with increased risk of in-hospital MAE, **Figure 3.5**.

The AUC for models 1, 2 and 3 were 0.62, 0.60 and 0.59, respectively, and they were not significantly different from each other. After 3-fold cross-validation with 100 repetitions, the average AUC and Brier score were 0.59 and 0.053, respectively, for model 1; 0.55 and 0.053, respectively, for model 2; 0.56 and 0.053, respectively, for model 3 (**Figure 3.5**).

3.4.4. Length of stay and costs

The overall mean of ranks for LOS was higher in women (Wilcoxon rank-sum test, P<0.001) and 18% of women stayed >1 day (range 2-27 days) as compared to 13% of men (range 2-33 days), P<0.001, **Table 3.1**. The occurrence of in-hospital MAE was associated with longer LOS in women and men compared to counterparts who did not experience MAE (median 4, IQR 2-6 days versus 1, IQR 1-1-day, and median 2, IQR 1-4 days versus 1, IQR 1-1-day, P<0.001 for both, respectively), **Table 3.2**. As expected, women and men who experienced in-hospital MAE had a significantly

higher index cost compared with those who did not have complications ($34,565, IQR $27,846-44,197 USD versus $24,078; IQR $18,581-$29,865 USD in women, and $30,405; IQR $22,381-36,418 USD versus $23,800; IQR $18,330-29,801 USD in men, P<0.001 for both sexes), **Table 3.2**.

3.5. Discussion

To the best of our knowledge, this is the first study to report sex-specific outcomes following LAAC. In this large cohort of 3294 who underwent LAAC, women comprised about 40%, and they experienced higher rates of in-hospital MAE compared with men. Women with higher CCI, ECS and CHA_2DS_2-VASc scores were more likely to experience in-hospital MAE, whereas non-whites and higher ECS were more likely to experience in-hospital MAE in men. Our findings provide significant implications for the understanding of how sex-related outcomes differ in patients undergoing LAAC.

3.5.1. Sex-related disparities and outcomes

Women are often underrepresented in clinical trials and among studies across a broad spectrum of health conditions, with sex differences observed in the prevalence, type of presentation and clinical outcomes.[21-23] The present study included 40% of women, and this is a higher proportion as compared with the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation)[24] and PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy)[25] trials (≈30% for both), and is in line with the EWOLUTION[26] (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the

WATCHMAN Left Atrial Appendage Closure Technology) registry and AMPLATZER Cardiac Plug[27] (ACP, St. Jude Medical, St. Paul, MN, USA) registries.

In this all-comer population, rates of cardiac complications were higher in both sexes, though markedly higher among women, compared with the PREVAIL,[25] ACP[27] and EWOLUTION studies.[26] Nonetheless, these findings are consistent with those observed in women after catheter ablation of AF.[28] Importantly, post-procedural stroke/TIA (0.4%) was lower than the observed in the PROTECT-AF[24] trial (1.1%) and ACP[27] registry (1.2%), and comparable with the PREVAIL[25] trial and EWOLUTION[26] registry. Of note, a subgroup analysis from a patient-level meta-analysis[13] pooling PROTECT-AF and PREVAIL data showed that there was no significant interaction between sex and treatment effect estimates in the composite efficacy endpoint. Although underpowered to draw strong conclusions, the present analysis is in agreement with those findings. Finally, we found very low rate of death in both sexes and this finding compares favorably with previous data.

3.5.2. Comorbidities and in-hospital complications

Despite the fact that women showed lower pre-procedural global measures of comorbidity burden than men, the proportion of women with in-hospital MAE increased with the increase in CCI and ECS, and so did men. These results are relevant since no data have shown sex-based differences in CCI and ECS and associated outcomes following LAAC.

We also found that the preprocedural thromboembolic risk as assessed by the CHA_2DS_2-VASc score was strongly associated with adverse outcomes following LAAC in women. Interestingly, our finding adds information to the above-mentioned patient-level meta-analysis[13] that showed no significant interaction among patients with CHA_2DS_2-VASc scores $\leq 3/>3$, and the findings of the EWOLUTION registry,[26] where there was no significant interaction among patients

with $CHADS_2$ <3/≥3 or CHA_2DS_2-VASc score <5/≥5 and the 7- and 30-day rate of serious adverse events after LAAC.

3.6. Limitations of the study

Our study has several limitations. The main limitation of this study lies in its observational nature. Second, based on an administrative database, coding errors may have occurred during data gathering, which represents a risk for ascertainment bias. Third, our outcomes were identified using ICD-10-CM codes (**Appendix D**), hence, albeit these codes were for post-LAAC complications, specific details such as the degree and severity of bleeds might not have been accurately captured. Pre-procedural bleeding risk (i.e. HAS-BLED score) could not be calculated due to the lack of specific variables. Fourth, the interruption of preprocedural oral anticoagulation has been associated as predictor of thromboembolic events; thus, data on anticoagulation status would have added important information in terms of bleeding and ischemic or thromboembolic complications beyond those inherent to the procedure. In this regard, we do not have data on in-hospital medications and periprocedural management of anticoagulation therapy, and this could have had an impact on certain outcomes such as bleeding or cerebrovascular accidents.[29, 30] Furthermore, post-procedural and discharge medications (i.e. oral anticoagulants with or without concomitant antiplatelets) management were not available. Hence, we were unable to adjust for residual confounders and the effect modification of unmeasured variables must be considered while interpreting our results. Finally, the study is limited to in-hospital outcomes, hence, we are unable to provide the impact of comorbid conditions on long-term follow-up, or the prevention of thromboembolism or hemorrhagic events by the LAAC.

3.7. Conclusion

This study represents a comprehensive appraisal on sex-related differences and outcomes following LAAC. Women experienced higher rates of in-hospital complications compared with men. Higher CCI, ECS and CHA_2DS_2-VASc score were associated with adverse outcomes in women, whereas higher ECS was associated with adverse outcomes in men. These findings are particularly relevant in the era of transcatheter-based cardiovascular interventions, adding new data to the structural heart interventional field. Further research is warranted to identify sex-specific pathways during patient's selection process to minimize complications in women undergoing LAAC.

3.8. Acknowledgment

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3.9. Competing interests

Dr Holmes is on the Advisory Board for Boston Scientific, unpaid. Dr Baron receives research support and have been on advisory board for Boston Scientific. The remaining authors of the study have no conflicts of interest inherent to the content of this manuscript.

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Table 3.1: Baseline characteristics and in-hospital outcomes of the study population

Patient characteristics	All n=3294	Women n=1313	Men n=1981	Adjusted P-value[#]
Mean age (years)	75.7±8.2	76.3±7.7	75.2±8.4	**<0.001**
Race*				
White	2738 (86)	1065 (85)	1673 (87)	**0.04**
Non-white	434 (14)	191 (15)	243 (13)	
Type of admission**				
Elective	2961 (90)	1173 (90)	1788 (91)	0.35
Non-elective	319 (10)	135 (10)	184 (9)	
Median household income***				
0-25th percentile	642 (20)	277 (21)	365 (19)	**0.02**
26-50th percentile	803 (25)	341 (26)	462 (24)	
51-75th percentile	926 (28)	361 (28)	565 (29)	
76-100th percentile	875 (27)	318 (25)	557 (28)	
Comorbidities				
Smoking	1123 (34)	355 (27)	768 (39)	**<0.001**
Dyslipidemia	1931 (59)	742 (56)	1189 (60)	0.05
Hypertension	2796 (85)	1117 (85)	1679 (85)	0.80
Diabetes mellitus	1092 (33)	381 (29)	711 (36)	**<0.001**
Previous PCI	63 (1.9)	15 (1.4)	48 (2.4)	**0.01**
Previous CABG	502 (15)	92 (7.0)	410 (21)	**<0.001**
Previous myocardial infarction	390 (12)	124 (9.4)	266 (13)	**0.001**
Congestive heart failure	1236 (38)	454 (35)	782 (39)	**0.01**
Valvular disease	680 (21)	277 (21)	403 (20)	0.60
Previous cerebrovascular disease	972 (30)	409 (31)	563 (28)	0.09
Peripheral vascular disease	355 (11)	121 (9.2)	234 (12)	**0.02**
Chronic pulmonary disease	695 (21)	319 (24)	376 (19)	**0.001**
Renal disease	709 (22)	242 (18)	467 (24)	**0.001**
Obesity	495 (15)	231 (18)	264 (13)	**0.001**
Peptic ulcer disease	41 (1.2)	20 (1.5)	21 (1.1)	0.24
Dementia	87 (2.6)	40 (3.1)	47 (2.4)	0.24
Rheumatic disease	97 (2.9)	66 (5.0)	31 (1.6)	**<0.001**
Liver disease	87 (2.6)	33 (2.5)	54 (2.7)	0.71
Hypothyroidism	542 (16)	322 (25)	220 (11)	**<0.001**
Coagulopathy	129 (3.9)	51 (3.9)	78 (3.9)	0.94
Cancer	73 (2.2)	22 (1.7)	51 (2.6)	0.09
Anemia	513 (16)	240 (18)	273 (14)	**0.001**
Depression	238 (7.2)	128 (9.7)	110 (5.5)	**<0.001**
Charlson comorbidity index	2.2±1.9	2.1±1.9	2.3±1.9	**0.01**
0	546 (17)	249 (19)	297 (15)	**0.003**
1	895 (27)	368 (28)	527 (27)	
2	670 (20)	265 (20)	405 (20)	
≥3	1183 (36)	431 (33)	752 (38)	
Elixhauser comorbidity score	9.7±5.8	9.3±5.9	9.9±5.7	**0.002**
≤0	37 (1.1)	19 (1.4)	18 (1.0)	**0.001**
1-5	1189 (36)	519 (40)	670 (34)	
6-10	672 (20)	267 (20)	405 (20)	

≥11	1396 (43)	508 (39)	888 (45)	
$CHADS_2$ score	2.7±1.3	2.7±1.3	2.7±1.3	0.96
≤1	522 (15)	226 (17)	296 (15)	0.08
≥2	2772 (85)	1087 (83)	1685 (85)	
CHA_2DS_2-VASc score	4.2±1.5	4.9±1.4	3.9±1.4	**<0.001**
≤1	56 (1.7)	<10 (0.2)	53 (2.7)	**<0.001**
≥2	3238 (98.3)	1310 (99.8)	1928 (97.3)	
Year of procedure				
2015 (October-December)	114 (3.5)	36 (2.7)	78 (3.9)	0.18
2016 (January-December)	1017 (31)	412 (31.4)	605 (30.6)	
2017 (January-December)	2163 (66)	865 (66)	1298 (66)	
In-hospital MAE	153 (4.6)	73 (5.6)	80 (4.0)	**0.04**
Bleeding complications	19 (0.6)	11 (0.8)	<10 (0.4)	0.11
Cardiac complications	55 (1.7)	31 (2.4)	24 (1.2)	**0.01**
Vascular complications	16 (0.5)	<10 (0.7)	<10 (0.4)	0.18
Stroke/TIA	14 (0.4)	<10 (0.6)	<10 (0.3)	0.19
Acute kidney injury	74 (2.2)	25 (1.9)	49 (2.5)	0.28
Length of stay (days)	1 (1-1)	1 (1-1)	1 (1-1)	**<0.001**
Length of stay (days, range)	0-33	0-27	0-33	---
≤1 day	2805 (85)	1080 (82)	1725 (87)	**<0.001**
>1 day	489 (15)	233 (18)	256 (13)	
Index admission cost[§], USD	24,143 (18,540-30,232)	24,340 (18,768-30,379)	23,951 (18,398-30,134)	0.13

Values are expressed as mean ± standard deviation, median (interquartile range) or % unless otherwise noted. Exact counts (n) for variables with <10 patients are not detailed as per the Healthcare Cost and Utilization Project data use agreement. [#]Adjusted p-values for each variable were computed from adjusting sampling design by discharge-level weights, cluster and strata. *Race was missing in 3.7%. **Type of admission was missing in 0.4%. ***Median household income was missing in 1.6%. [§]Index admission cost was missing 0.3%. CABG: coronary artery bypass surgery. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack (TIA), Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category. MAE: major adverse event. USD: United States dollar.

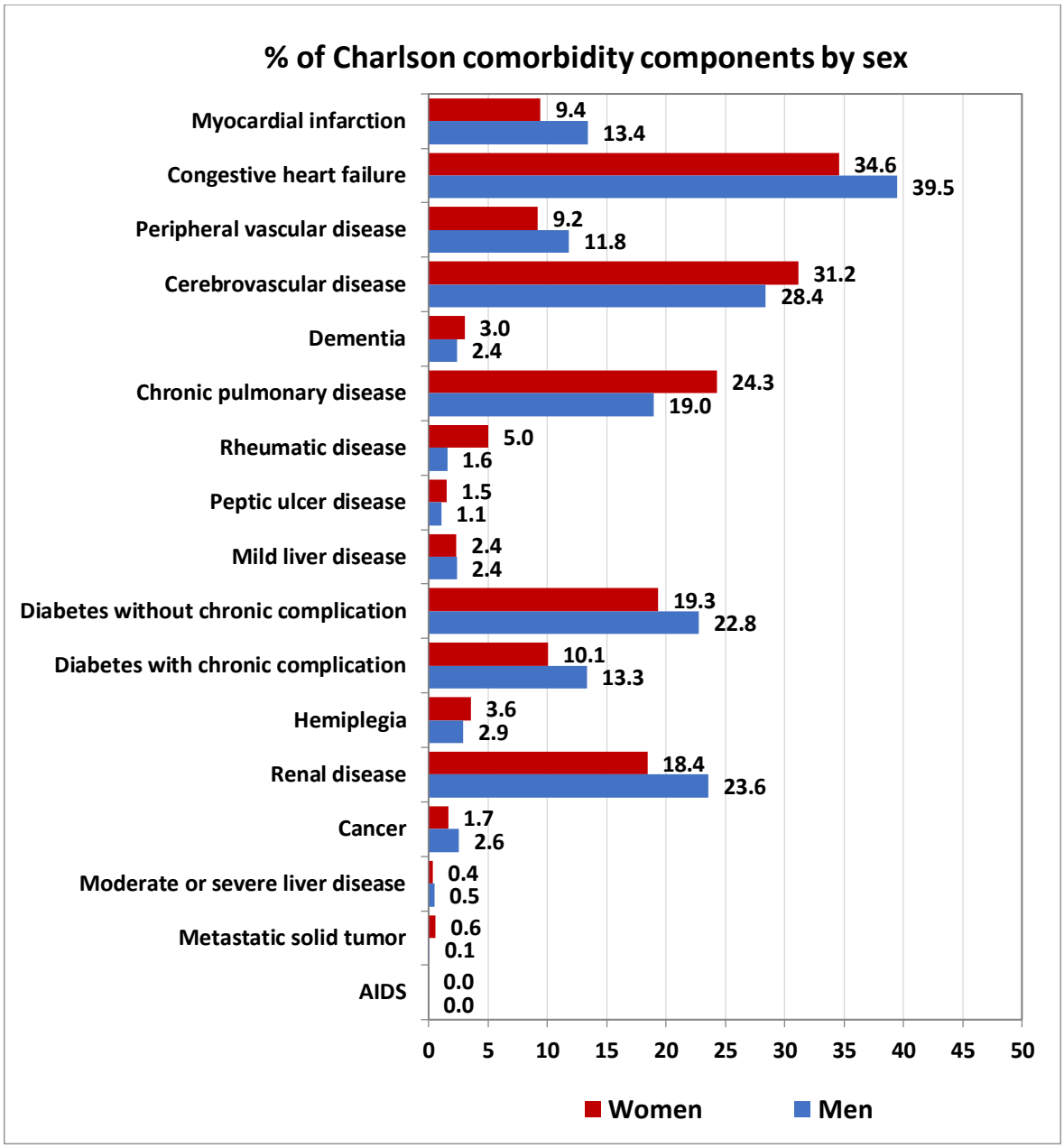
Table 3.2: Baseline characteristics of women and men according to the occurrence of in-hospital MAE

Patients characteristics	Women (n=1313)			Men (n=1981)				
	With in-hospital MAE n=73	Without in-hospital MAE n=1240	Adjusted P-value[#]	With in-hospital MAE n=80	Without in-hospital MAE n=1901	Adjusted P-value[#]	Adjusted P-value[¶]	Adjusted P-value[¥]
Mean age (years)	77.1±7.4	76.2±7.7	0.32	75.1±8.6	75.2±8.4	0.86	0.10	**0.001**
Race*								
White	59 (83)	1006 (85)	0.68	62 (79)	1611 (88)	**0.03**	0.57	**0.03**
Non-white	12 (17)	179 (15)		16 (21)	227 (12)			
Median household income**								
0-25th percentile	14 (20)	263 (21)	0.72	13 (17)	352 (19)	0.70	0.81	**0.01**
26-50th percentile	15 (21)	326 (27)		20 (26)	442 (23)			
51-75th percentile	21 (30)	340 (28)		25 (33)	540 (29)			
76-100th percentile	20 (29)	298 (24)		18 (24)	539 (29)			
Comorbidities								
Smoking	20 (27)	335 (27)	0.94	23 (29)	745 (39)	0.06	0.85	**<0.001**
Dyslipidemia	49 (67)	693 (56)	0.06	46 (58)	1143 (60)	0.64	0.21	**0.02**
Hypertension	63 (86)	1054 (85)	0.76	66 (83)	1613 (85)	0.57	0.54	0.91
Diabetes mellitus	24 (33)	357 (29)	0.45	31 (39)	680 (36)	0.59	0.47	**<0.001**
Previous PCI	<10 (2.7)	13 (1.1)	0.19	<10 (0)	48 (2.5)	0.15	0.13	**0.003**
Previous CABG	<10 (11)	84 (6.8)	0.18	16 (20)	394 (21)	0.88	0.14	**<0.001**
Previous myocardial infarction	13 (18)	111 (9.0)	**0.01**	10 (13)	256 (13)	0.80	0.34	**<0.001**
Congestive heart failure	35 (48)	419 (34)	**0.01**	42 (53)	740 (39)	**0.01**	0.58	**0.003**
Valvular disease	18 (25)	259 (21)	0.44	16 (20)	387 (20)	0.94	0.51	0.72
Previous cerebrovascular disease	22 (30)	387 (31)	0.85	13 (16)	550 (29)	0.01	**0.03**	0.17
Peripheral vascular disease	18 (25)	103 (8.3)	**<0.001**	11 (14)	365 (19)	0.22	**0.03**	**0.002**
Chronic pulmonary disease	21 (29)	298 (24)	0.36	<10 (11)	225 (12)	0.87	**0.02**	**0.001**
Renal disease	23 (32)	219 (18)	**0.003**	27 (34)	440 (23)	**0.03**	0.77	**0.002**
Obesity	13 (18)	218 (18)	0.96	14 (18)	250 (13)	0.26	0.96	**0.001**
Peptic ulcer disease	<10 (1.4)	19 (1.5)	0.91	<10 (1.3)	20 (1.1)	0.87	0.95	0.23
Dementia	<10 (8.2)	34 (2.7)	**0.01**	<10 (3.8)	44 (2.3)	0.44	0.22	0.45
Rheumatic disease	<10 (4.1)	63 (5.1)	0.71	<10 (2.5)	29 (1.5)	0.49	0.57	**<0.001**
Liver disease	<10 (0)	33 (2.7)	0.15	<10 (1.3)	53 (2.8)	0.41	0.34	0.83
Hypothyroidism	19 (26)	303 (24)	0.76	10 (13)	210 (11)	0.69	**0.03**	**<0.001**
Coagulopathy	<10 (5.5)	47 (3.8)	0.47	12 (15)	66 (3.5)	**<0.001**	0.05	0.64

Cancer	<10 (2.7)	20 (1.6)	0.47	<10 (1.3)	50 (2.6)	0.45	0.51	**0.06**
Anemia	23 (32)	217 (18)	**0.002**	26 (33)	247 (13)	**<0.001**	0.90	**<0.001**
Depression	<10 (9.6)	121 (9.8)	0.96	<10 (2.5)	108 (5.7)	0.22	0.06	**<0.001**
Charlson comorbidity index	3.0±2.2	2.1±1.9	**0.001**	2.5±1.8	2.3±1.8	0.42	0.11	**0.002**
0	<10 (10)	242 (20)		11 (14)	286 (15)			
1	17 (23)	351 (28)	**0.03**	18 (22)	509 (27)	0.48	0.87	**0.001**
2	15 (21)	250 (20)		14 (17)	391 (20)			
≥3	34 (46)	397 (32)		37 (47)	715 (38)			
Elixhauser comorbidity score	11.0±6.2	9.2±5.9	**0.02**	11.4±5.6	9.9±5.7	**0.03**	0.73	**0.001**
≤0	<10 (1.3)	18 (1.5)		<10 (1.3)	17 (0.9)			
1-5	20 (28)	499 (40)	0.15	14 (17)	656 (35)	**0.02**	0.54	**0.001**
6-10	16 (22)	251 (20)		20 (25)	385 (20)			
≥11	36 (49)	472 (38)		45 (57)	843 (44)			
$CHADS_2$ score	3.0±1.3	2.7±1.3	0.15	2.6±1.2	2.7±1.2	0.29	0.08	0.66
≤1	10 (14)	216 (17)	0.41	65 (19)	281 (15)	0.33	0.41	**0.05**
≥2	63 (86)	1024 (83)		15 (81)	1620 (85)			
CHA_2DS_2-VASc score	5.3±1.5	4.8±1.4	**0.01**	3.7±1.4	3.9±1.4	0.35	**<0.001**	**<0.001**
≤1	0 (0)	<10 (0.2)		<10 (3.8)	50 (2.6)	0.54	0.09	**<0.001**
≥2	73 (100)	1237 (99.8)	0.67	77 (96)	1851 (97)			
Year of procedure								
2015 (October-December)	<10 (6.8)	31 (2.5)		<10 (6.3)	73 (3.8)			
2016 (January-December)	412 (26)	393 (32)	0.06	26 (33)	579 (30)	0.49	0.67	0.10
2017 (January-December)	865 (67)	816 (66)		49 (61)	1249 (66)			
Length of stay (days)	4 (2-6)	1 (1-1)	**<0.001**	2 (1-4)	1 (1-1)	**<0.001**	**0.003**	**0.01**
≤1 day	12 (16)	1068 (86)	**<0.001**	31 (39)	1694 (89)	**<0.001**	**0.002**	**0.01**
>1 day	61 (84)	172 (14)		49 (61)	207 (11)			
Index admission cost[§], USD	34,565 (27,846-44,197)	24,078 (18,581-29,865)	**<0.001**	30,405 (22,381-36,418)	23,800 (18,330-29,801)	**<0.001**	**0.01**	0.42

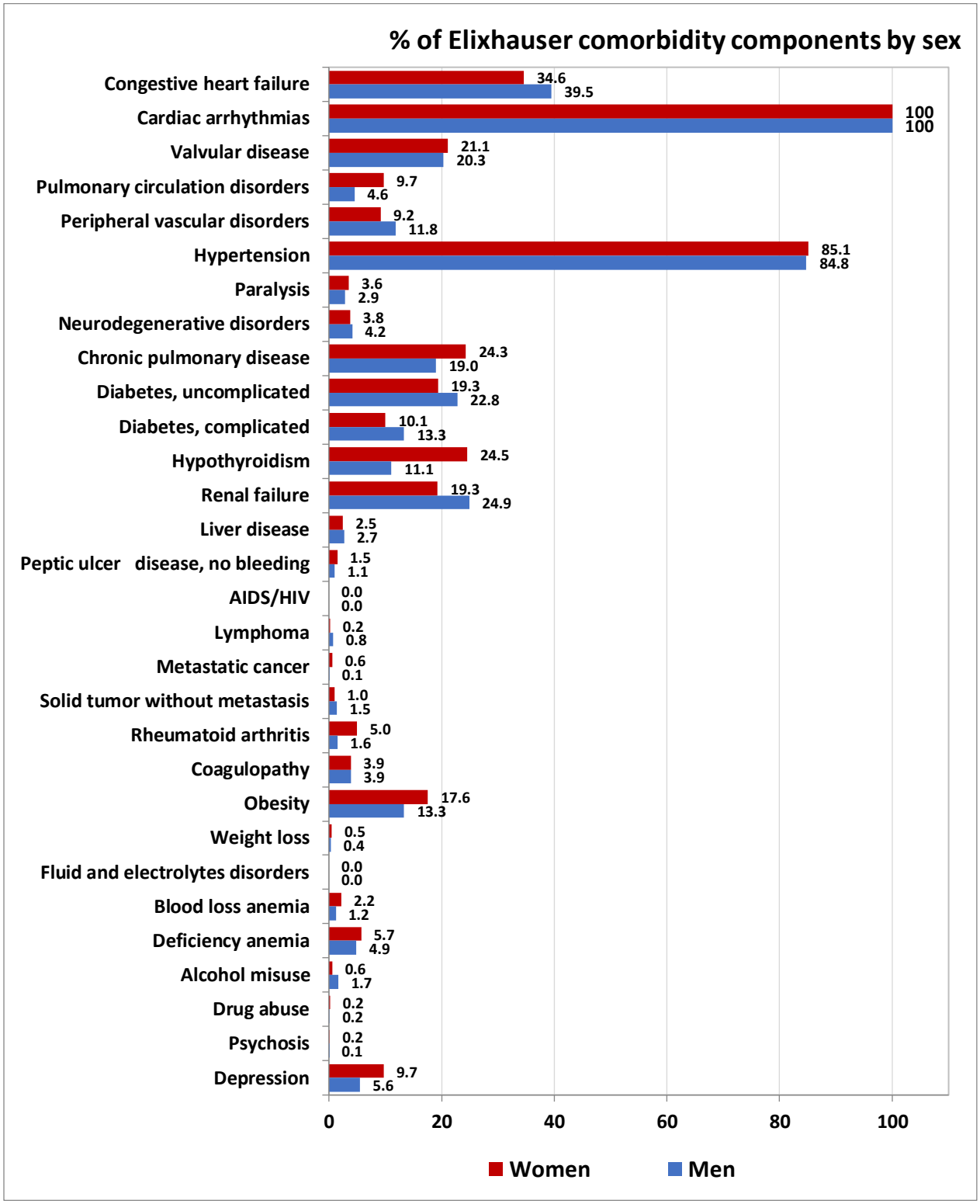
Values are expressed as mean ± standard deviation, median (interquartile range) or n (%) unless otherwise noted. Exact counts (n) for variables with <10 patients are not detailed as per the Healthcare Cost and Utilization Project data use agreement. *Race was missing 4.3% in women cohort and 3.3% in men cohort. **Median household income was missing 1.2% in women cohort and 1.6% in men cohort. [§]Index admission cost was missing 0.2% in women cohort and 0.4% in men cohort. [#]Adjusted P-values for each variable were computed from adjusting sampling design by discharge-level weights, cluster and strata. Differences between women and men with ¶ and without ¥ in-hospital major adverse event (MAE). CABG: coronary artery bypass surgery. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack, Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category. USD: United States dollar

Figure 3.1: Proportion of components in Charlson Comorbidity Index according to sex.



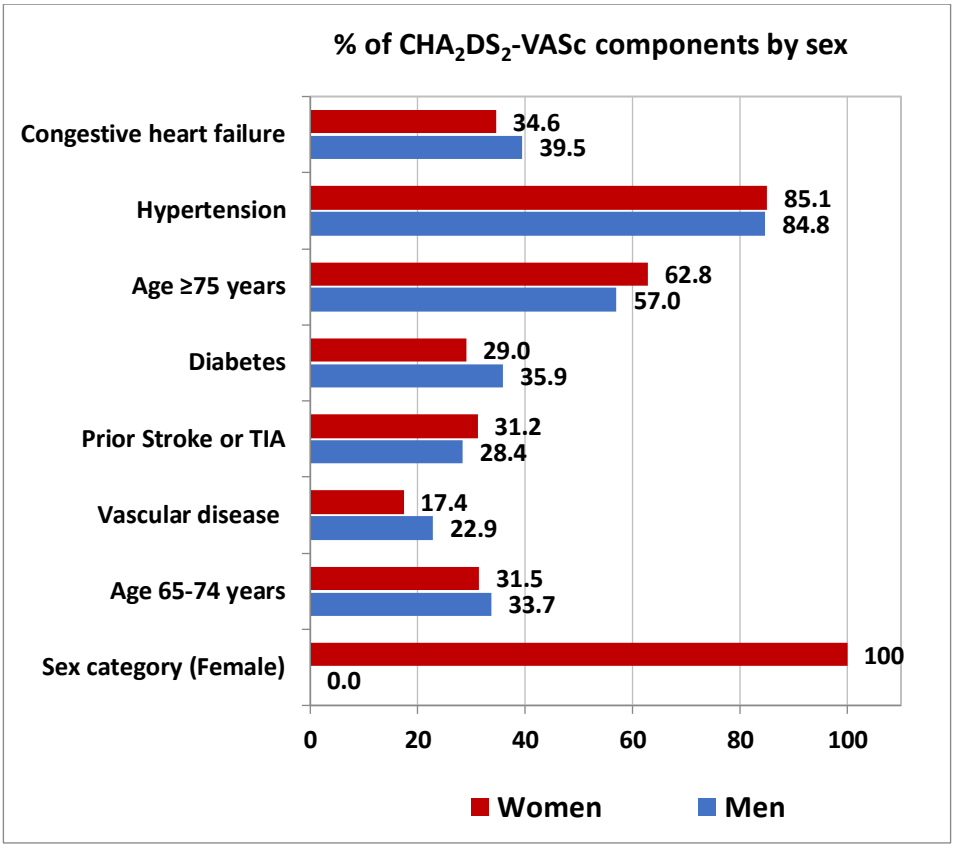
AIDS: acquired immune deficiency syndrome, HIV: human immunodeficiency virus infection.

Figure 3.2: Proportion of components in Elixhauser Comorbidity Score according to sex.



AIDS: acquired immune deficiency syndrome, HIV: human immunodeficiency virus infection.

Figure 3.3: Proportion of components in CHA_2DS_2-VASc score according to sex.



CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack, Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category.

Figure 3.4: Temporal trends in left atrial appendage closure procedures performed quarterly and in-hospital complications from 2015-2017 according to sex.

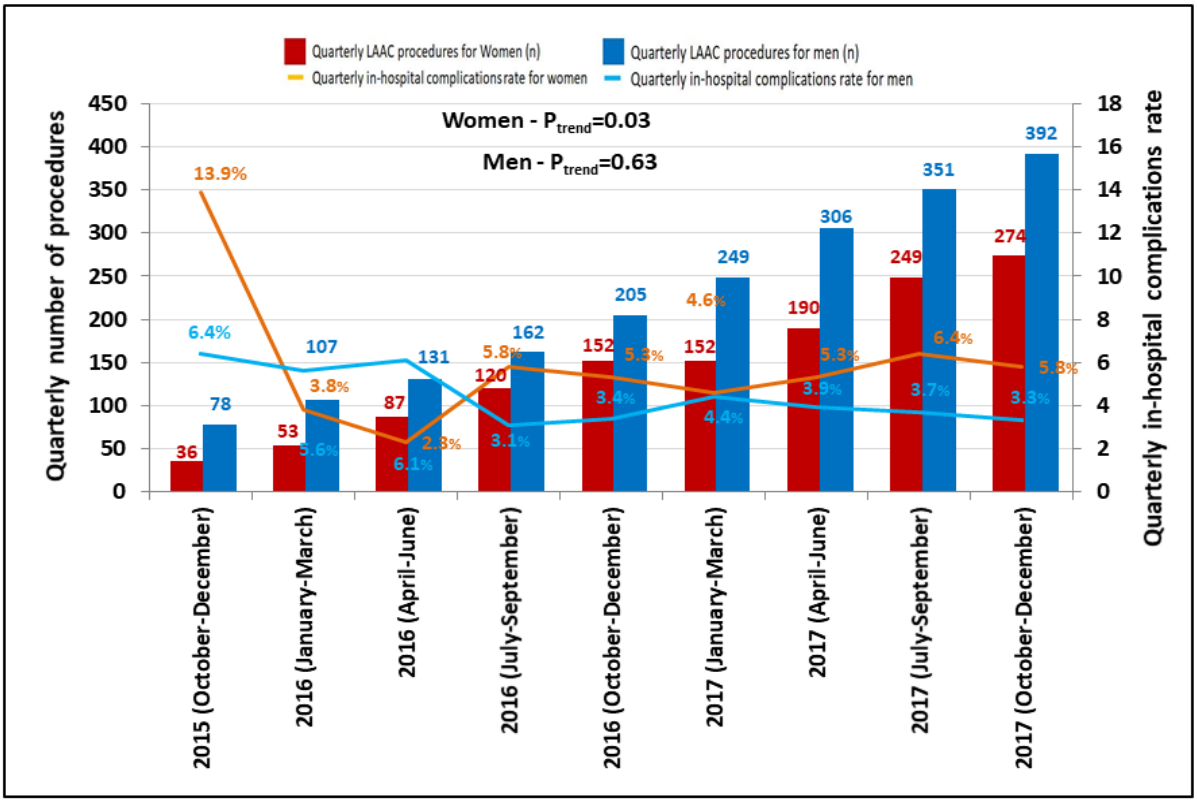
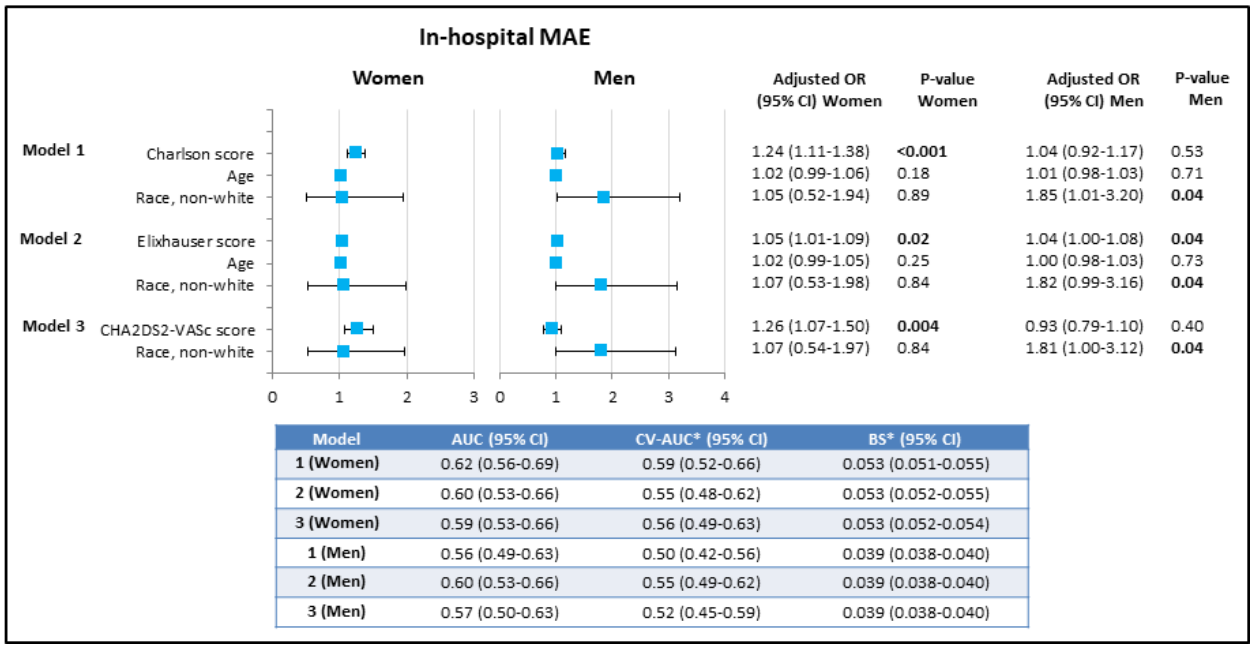


Figure 3.5: Multivariable logistic regression analyses of factors associated with in-hospital MAE according to sex



Model	AUC (95% CI)	CV-AUC* (95% CI)	BS* (95% CI)
1 (Women)	0.62 (0.56-0.69)	0.59 (0.52-0.66)	0.053 (0.051-0.055)
2 (Women)	0.60 (0.53-0.66)	0.55 (0.48-0.62)	0.053 (0.052-0.055)
3 (Women)	0.59 (0.53-0.66)	0.56 (0.49-0.63)	0.053 (0.052-0.054)
1 (Men)	0.56 (0.49-0.63)	0.50 (0.42-0.56)	0.039 (0.038-0.040)
2 (Men)	0.60 (0.53-0.66)	0.55 (0.49-0.62)	0.039 (0.038-0.040)
3 (Men)	0.57 (0.50-0.63)	0.52 (0.45-0.59)	0.039 (0.038-0.040)

MAE: major adverse events. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack, Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category. aOR: adjusted odds ratio. CI: confidence interval. AUC: area under receiver operating curve. CV-AUC: cross-validation AUC. BS: Brier score. Models 1, 2 and 3 were adjusted by age, race and Charlson-weighted score, age, race and Elixhauser-weighted score and race and CHA_2DS_2-VASc score, respectively. For continuous variables, the aOR are per unit of increase in each of the predictive factors. CV-AUC* and BS* were computed through 3-fold cross validation with 100 repetitions. Lower (close to 0) values of Brier score indicate better fit of the model. Blue squares with whiskers denote the OR and its CI of in-hospital MAE.

Chapter 4

Outcomes of Patients ≥80 years of Age Undergoing Left Atrial Appendage Closure

4.1. Abstract

Background: Patients referred for left atrial appendage closure (LAAC) present with overlapping risks of systemic thromboembolism and bleeding. Elderly patients have a higher burden of comorbidities and frailty, both of which influence clinical outcomes. We aimed to compare in-hospital outcomes in patients ≥80 years to younger patients, and to determine whether global measures of comorbidity burden and frailty assessment are associated with increased risk of adverse events after LAAC.

Methods: The National Inpatient Sample (NIS) was used to identify discharges after LAAC between October 2015 and December 2017. The primary outcome was in-hospital major adverse events (MAE) defined as the composite of bleeding complications, acute kidney injury, vascular complications, cardiac complications and post-procedural stroke. Comorbidity burden was assessed by the Charlson comorbidity index (CCI) and Elixhauser comorbidity score (ECS). The Hospital Frailty Risk Score (HFRS) was used as a measure of frailty. The association of comorbidity and frailty with in-hospital MAE was evaluated using logistic regression models for patients aged ≥80 years and <80 years, respectively.

Results: 3294 subjects were identified, of whom, 1089 (33%) were ≥80 years and 2205 (67%) <80 years old. Overall, 86% of patients were at low risk of frailty (HFRS <5) and ≥80 years patients had higher HFRS compared with <80 years old (median 1.6, inter-quartile range [IQR] 0.4-3.7 versus median 1.5, IQR 0-3.3, P=0.04). Patients ≥80 years showed a lower CCI (2.1±1.8 versus 2.3±1.9, P=0.02), a similar ECS and higher CHA_2DS_2-VASc score (4.7±1.4 versus 4.1±1.5,

P<0.001) compared with <80 years counterparts. Patients ≥80 years experienced a similar rate of MAE compared to those aged <80 years (5.1% versus 4.4%, P=0.34). In patients ≥80 years, female sex had 1.8-fold higher odds of MAE, and increase in CCI (adjusted odds ratio [aOR]): 1.20, 95% confidence interval [CI]: 1.05-1.36, P=0.01) and HFRS (aOR: 1.17, 95% CI: 1.09-1.25, P<0.001) were also associated with higher risk of in-hospital MAE. In patients <80 years old, per-unit increase in CCI (aOR: 1.11, 95% CI: 1.00-1.22, P=0.04), ECS (aOR: 1.04, 95% CI: 1.01-1.08, P=0.01) and HFRS (aOR: 1.18, 95% CI: 1.11-1.25, P<0.001) were associated with increased risk of in-hospital MAE.

Conclusion: Patients ≥80 years had similar rates of in-hospital MAE compared to patients aged <80 years. The HFRS appears to provide valuable information for the prediction of in-hospital complications in patients undergoing LAAC.

Key words: elderly, frailty, octogenarians, atrial fibrillation, stroke, anticoagulation, bleeding, left atrial appendage closure

4.2. Introduction

The prevalence of atrial fibrillation (AF) increases with age,[1] as does the risk of cerebrovascular accidents.[2-5] Moreover, those over the age of 80 years have >20% of AF-related strokes[5] and these are often more severe in terms of disability and mortality.[5-7] Whilst oral anticoagulation therapy is the mainstay for stroke prevention,[6, 8] elderly patients are at increased risk of bleeding events;[3, 9] hence, these drugs are often underused, mainly because of advanced age or perceived risk of bleeding complications, falls or polypharmacy.[3, 6, 7, 10]

Studies have demonstrated the safety and efficacy of left atrial appendage closure (LAAC) to reduce the risk of stroke in patients with AF,[11-13] and current guidelines recommend LAAC for individuals in whom long-term oral anticoagulation is considered either sub-optimal or contraindicated.[6, 8] Patients referred for LAAC often present with overlapping risks of systemic thromboembolism and bleeding events. In addition, elderly patients are generally more frail and have higher comorbidity burden, both of which often co-exist and influence clinical outcomes.[14-18] Therefore, we aimed to compare in-hospital outcomes in patients ≥80 years to younger patients, and to determine whether global measures of comorbidity burden and frailty assessment are associated with increased risk of adverse events after LAAC.

4.3. Methods

4.3.1. Data Source and Study Population

We conducted a cohort-based observational study using the National Inpatient Sample (NIS) database, a nationally representative and all-payer publicly available database of hospitalized patients in the United States. The NIS database was developed by the Agency for Healthcare Research and Quality (AHRQ) as a part of Healthcare Cost and Utilization Project (HCUP), which includes hospital information for more than 7 million hospital discharges annually and

approximately 20% stratified weighted sample of all discharges from United States community hospitals.[19]

Between October 2015 and December 2017, hospitalizations for LACC, as a primary procedure, were identified using the international Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) procedure code 02L73DK (occlusion of left atrial appendage with intraluminal device, percutaneous approach). For this study, individuals were divided into two groups, those with an age ≥80 years old and those <80 years old, and ICD-10-CM codes were used to obtain patient's demographics and, among others, the CHA_2DS_2-VASc score to estimate the preprocedural thromboembolic risk of participants.

4.3.2. Comorbidity burden and frailty measures

ICD-10-CM codes were used to identify comorbidities required to calculate comorbidity burden and frailty scoring systems. Comorbidity burden was identified using two validated comorbidity scoring systems, the Charlson comorbidity index (CCI)[20] and Elixhauser comorbidity score (ECS).[21] The CCI consists of 17 comorbidities and each of them has an associated weighting without age, which is summed across the 17 conditions to define the total CCI score (scale 0 to 29) (**Appendix A**). The ECS consists of 30 comorbidity measures and its modification into a point system[22] (scale -19 to 89) was adopted for this study (**Appendix B**).

The Hospital Frailty Risk Score (HFRS)[17] was used to investigate the presence and degree of frailty and calculated from 109 ICD-10-CM codes (**Appendix C**). According to Gilbert et al.,[17] patients were divided into 3 categories based on individual HFRS as low (<5), intermediate (5-15) and high risk (>15 HFRS) of frailty, and those presenting with intermediate and high HFRS were considered a frail.

4.3.3. Study Outcomes

The primary outcome of interest was the occurrence of in-hospital major adverse events (MAE). In-hospital MAE were identified using 10-CM codes and detailed in **Appendix D,** and this included a composite of post-procedural bleeding complications, acute kidney injury, cardiovascular complications, vascular complications and stroke or transient ischemic attack (TIA).

4.4. Statistical Analysis

Categorical variables are shown as counts and percentages and continuous variables are presented as mean ± standard deviation or median (inter-quartile range [IQR]) according to variable distribution. Because of Healthcare Cost and Utilization Project data use agreement, variables in tables with less than 10 discharge records are displayed as "<10". Differences between patients ≥80 years and <80 years were evaluated using two-sided Student's t-test or Wilcoxon rank-sum test for continuous variable and the chi-square test for categorical variables, accordingly, adjusting for a survey sampling design. P-values for each variable were computed adjusting for sampling discharge-level weights, cluster and strata provided by NIS and recommended by AHRQ during survey-specific analysis.

The Cochran-Armitage trend test was used for detecting differences in trends for complications over the time. Length of stay was computed by subtracting the admission date from the discharge date. Hospital volumes were determined based on the annual number of LAAC performed by each hospital in a given year.

Factors associated with the primary outcome for patients ≥80 years and <80 years were assessed separately. We first conducted the univariate analysis for each outcome with a single variable, then, the variables associated with outcome variable from univariate analysis with a P-value of <0.10 were included in multivariable models along with each scoring system (CCI, ECS

and HFRS). In addition, clinically relevant variables such as age and race were also included in multivariable models. The association between the probability of in-hospital MAE and CCI, ECS and HFRS is presented graphically using restricted cubic splines with 5 knots.[23]

To account for the two-level hierarchical structure of NIS database (patients are nested within hospitals), multilevel modeling was applied allowing the intercepts to vary across hospitals. The variances of the random-effect were all close to zero after fitting multilevel logistic regression models for in-hospital MAE. Therefore, multivariable logistic regression models were fitted for the whole cohort to evaluate the association of age (<80 and ≥80 years) as well as the CCI, ECS and HFRS scores with in-hospital MAE. To further evaluate the association of the CCI, ECS and HFRS scores with in-hospital MAE, multivariable logistic regression models were fitted separately for patients ≥80 years and <80 years. Each of the multivariable models included sex, race and CCI-weighted (model 1), ECS-weighted (model 2) and HFRS-weighted (model 3), respectively. We adjusted for age in the whole cohort but not thereafter upon dichotomization.

Area under the receiver operating characteristic curve (AUC) analysis was conducted for each model to assess its discrimination ability for in-hospital MAE. The goodness-of-fit of the model was differentiated according to Akaike information criterion (AIC) and comparatively, a lower AIC indicates a model fits the data better. Initially, the base model was adjusted by age, sex and race, thereafter, models 1, 2, and 3 were compared with the base model. We used likelihood ratio test (LRT) and integrated discrimination improvement (IDI) test for evaluating improvement in the model's performance compared to the base model. Model's calibration was assessed by the Brier score that was calculated from mean squared error of prediction for each model. Statistically significant differences were considered at P-values of <0.05. All statistical analysis were preformed using R version 3.6.1.[24]

4.5. Results

4.5.1. Study population

A total of 3294 hospitalizations were identified in the NIS dataset as having undergone LAAC as a primary procedure. Of these, 1089 (33%) were ≥80 years old (mean age 84.1±3.0 years) and 2205 (67%) were <80 years old (mean age 71.5±6.5 years). Remaining baseline characteristics are presented in **Table 4.1**. Interestingly, the mean CCI was lower in patients ≥80 years compared with <80 years old (2.1±1.8 versus 2.3±1.9, P=0.02) while having similar mean ECS. The group-based distribution of CCI and ECS are presented in **Supplementary Figures 4.1** and **4.2**, respectively. Low (<5) and intermediate (5-15) HFRS were encountered in 85% and 14% of patients ≥80 years and 87% and 13% of <80 years old, respectively. Compared to <80 years old, patients ≥80 years showed overall higher HFRS (median 1.6, IQR 0.4-3.7 versus median 1.5, IQR 0-3.3, P=0.04), **Table 4.1**. Patients ≥80 years showed higher CHA_2DS_2-VASc score (4.7±1.4 versus 4.1±1.5, P<0.001) and 100% of them presented with a high pre-procedural thromboembolic risk (CHA_2DS_2-VASc score ≥2) while 97.5% in the <80 years old cohort did (**Table 4.1**).

4.5.2. In-hospital outcomes

The composite of in-hospital MAE occurred in 4.6% of patients, without statistical differences between patients ≥80 years and <80 years (5.1% versus 4.4%, P=0.34) (**Table 4.1**). Overall death occurred in 0.2% of cases, 0.3% in those aged ≥80 years and 0.1% in <80 years old.

A quarterly analysis indicates that the number of LAAC procedures increased over time. While the incidence of in-hospital MAE decreased from 16.7% in October-December 2015 to 4.9% in October-December 2017 in patients ≥80 years, and from 6.0% to 4.1% in <80 years old, **Figure 4.1**; however, without statistical significance (P=0.16 for patients ≥80 years and P=0.32 for <80 years old) based on the Cochran Armitage trend test.

To further evaluate the factors associated with in-hospital MAE, patient's demographic and procedural characteristics according to age ≥80 and <80 years old are detailed in **Table 4.2**. In both cohorts, the proportion of patients with in-hospital MAE increased with the increase in comorbidity burden (CCI 2.7±2.0 versus 2.1±1.8, P=0.02 in patients ≥80 years and CCI 2.7±2.0 versus 2.3±1.9, P=0.04, and ECS 11.3±6.2 versus 9.6±5.9, P=0.01 in <80 years old). The HFRS was also higher among patients ≥80 years and <80 years old with in-hospital MAE (median 3.0, IQR 1.4-5.8 versus median 1.5, IQR 0.4-3.6, P=0.01 and median 3.3, IQR 1.6-5.4 versus median 1.5, IQR 0-3.2, P<0.001, respectively, **Table 4.2**. The probability of in-hospital complications increased with the increase in CCI, ECS and HFRS, **Figure 4.2**.

4.5.3. Length of hospital stay and cost

The overall median LOS was similar for patients ≥80 years and <80 years (P=0.15), **Table 4.1**. The LOS was significantly longer among ≥80 years and <80 years old who experienced in-hospital MAE compared to counterparts who did not experience in-hospital MAE (Wilcoxon rank-sum test, P<0.001, for both). Patients ≥80 years and <80 years who experienced in-hospital MAE had a significantly higher index cost compared with those who did not have complications ($32,671; IQR $21,342-38,234 USD versus $23,939; IQR $18,701-28,949 USD and $33,014; IQR $25,888-39,330 USD versus $23,911; IQR $18,343-30,112 USD, respectively), **Table 4.2**.

4.5.4. Factors associated with in-hospital complications

After adjusting for age, sex, race, CCI-weighted, ECS-weighted and HFRS-weighted, the risk of in-hospital MAE for the whole cohort was higher in women (~1.4-fold), per-unit of increase in CCI (OR: 1.14, 95% CI: 1.05-1.23), ECS (OR: 1.04, 95% CI: 1.02-1.1.07) and HFRS (OR: 1.17 95% CI: 1.12-1.23). Notably, age ≥80 years old was not significantly associated with higher risk of in-

hospital MAE (OR: 1.26, 95% CI: 0.89-1.77, P=0.19), **Figure 4.3**. Among patients ≥80 years, women had ~1.8-fold higher odds of in-hospital MAE as well as patients with higher CCI (OR: 1.20 95% CI: 1.05-1.36) and HFRS (OR: 1.17 95% CI: 1.09-1.25). In patients <80 years, higher risk of in-hospital MAE was associated with per unit of increase in CCI (OR: 1.11 95% CI: 1.00-1.22), ECS (OR: 1.04 95% CI: 1.01-1.1.08) and HFRS (OR: 1.18 95% CI: 1.11-1.25), **Figure 4.3**.

Compared to the base model and the CCI-based and ECS-based models, the HFRS-based model showed better discrimination ability and goodness-of-fit for the occurrence of in-hospital MAE as indicated by AUC and AIC. Moreover, model's performance and calibration showed higher LRT and lower Brier scores, indicating therefore, that the HFRS-based model fits the data better, **Figure 4.3**.

4.6. Discussion

In this cohort of 3294 hospitalizations for LAAC, close to one in three patients were ≥80 years and, therefore, represents one of the largest cohort of patients ≥80 years of age who underwent LAAC. The overall cohort presented with high burden of comorbidities, however, most of the patients were at low risk for frailty as assessed by a HFRS <5. Patients ≥80 years experienced similar composite in-hospital complication rates as compared with patients <80 years. Female sex and increase in CCI and HFRS were associated with increased risk of in-hospital MAE in patients ≥80 patients, whereas higher CCI, ECS and HFRS were associated with increased risk of in-hospital MAE in patients <80 years. The addition of HFRS to the models appears to fit the data better for the prediction of in-hospital adverse events after LAAC, however, one needs to interpret these findings with caution given that the discriminative ability of the HFRS model over the CCI and ECS may not strongly translate into clinical importance.

These findings are important since elderly patients are often underrepresented in clinical trials and across a broad spectrum of health conditions, with marked disparities in the type of presentation, and clinical outcomes.[35, 36] In our study presenting national estimates in which one-third of the patients were ≥80 years of age, the overall number of patients who have undergone LAAC has increased, while in-hospital MAE appear to have improved over the time.

4.6.1. Factors associated with in-hospital adverse events

Studies have shown that among individuals aged ≥80 years of age, more than 80% of this population present with multiple comorbid conditions, and comorbidity burden is a strong predictor of poor outcomes.[25] The CCI and ECS scores are global measures of comorbidity burden that have previously been validated for estimating clinical outcomes and prognosis among individuals undergoing coronary and valvular heart interventions.[15, 26-29] Our results indicate that comorbidity burden as assessed by the CCI was independently associated with in-hospital MAE.

There is growing evidence that frailty is an important predictor of adverse outcomes in the elderly population and across a number of cardiovascular conditions and interventions.[18, 30-32] In this study, we used the HFRS as a measure of frailty who underwent LAAC in the United States. Our findings suggest that the HFRS outperforms global measures of comorbidity such as the CCI for its association with in-hospital adverse events; however, as above mentioned, the overall predictive ability of the models was modest, and whether these differences are clinically meaningful is to be determined in future larger studies.

4.6.2 Comparison with other studies

The HFRS was developed and validated in individuals ≥75 years old in the United Kingdom,[17] and more than 30 tools for assessing frailty have been proposed and developed; however, there is a lack of agreement between these different tools and thus, some patients may be incorrectly classified

with frailty status.[30, 33] In this regard, the original validation of the HFRS[17] showed low degree of agreement when compared with a Fried frailty criteria (≥3 items present, kappa-score 0.22, 95% CI 0.15-0.30) and Rockwood classification (cutoff of 0.25, kappa-score 0.30, 95% CI 0.22-0.38). Moreover, participants with HFRS between 5 and 15 (intermediate and high risk of frailty), only 40% were classified as frail by Rockwood.[17] This disagreement could, in part, have been related to the categorization of a continuous variable and assuming a linear association of a continuous variable.[34] In our study, the vast majority of the patients presented with low risk of frailty (HFRS <5); however, we used the HFRS as a continuous variable and those with higher HFRS were associated with higher rates of in-hospital MAE (**Figures 4.2** and **4.3**). Therefore, our study provides new insights on the potential additional information of adding the HFRS to help stratify frailty and its associated risk of adverse outcomes among patients undergoing LAAC.

4.7. Strengths and limitations

The strength of our analysis lies in its large sample size, and the first study to appraise the clinical impact of pre-procedural comorbidity burden and frailty status in patients ≥80 years undergoing LAAC.

This study presents with limitations. The main limitation lies in its observational nature and reliance on an administrative claims database, and errors while coding may have occurred and therefore affected data gathering and inability to adjust for unmeasured confounders. Even though event rates after LACC were relatively low and thus had to be pooled for a composite endpoint, post procedural MAE are not well adjudicated in NIS. Second, pre-procedural bleeding risk (i.e. HAS-BLED score) could not be calculated due to the lack of specific variables. Third, periprocedural management of anticoagulation therapy was not available and this might have

impacted certain outcomes such as bleeding or cerebrovascular accidents. Finally, because this dataset only includes in-hospital information, we were unable to ascertain the impact of comorbidity burden and frailty on long-term outcomes and readmission rates.

4.8. Conclusion

In this cohort-based study including a large number of patients ≥80 years who underwent LAAC, the rates of in-hospital MAE were similar compared to patients <80 years. The addition of the HFRS over global measure of comorbidity burden appears to provide valuable insight into the prediction of in-hospital adverse events. Further, adequately powered research is needed to ascertain the impact of adding the HFRS on patient-important outcomes during the clinical decision making of patients undergoing LAAC.

4.9. Acknowledgment

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4.10. Competing interests

Dr Holmes is on the Advisory Board for Boston Scientific, unpaid. Dr Baron receives research support and have been on advisory board for Boston Scientific. The remaining authors of the study have no conflicts of interest inherent to the content of this manuscript.

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Racial/Ethnic Minority Groups in Contemporary Acute Coronary Syndrome Clinical Trials: A Systematic Review. *JAMA Cardiol*. 2020.

Table 4.1: Baseline characteristics and in-hospital outcomes of the study population

Patient characteristics	All n=3294	≥80 years n=1089	<80 years n=2205	Adjusted P-value[#]
Mean age (years)	75.7±8.2	84.1±3.0	71.5±6.5	**<0.001**
Women	1313 (40)	467 (43)	846 (38)	**0.01**
Race*				
White	2738 (86)	924 (88)	1814 (85)	**0.03**
Non-white	434 (14)	124 (12)	310 (15)	
Type of admission**				
Elective	2961 (90)	981 (91)	1980 (90)	0.60
Non-elective	319 (10)	101 (9.3)	218 (10)	
Median household income***				
0-25th percentile	642 (20)	190 (18)	452 (21)	0.20
26-50th percentile	803 (25)	268 (25)	535 (25)	
51-75th percentile	926 (28)	314 (29)	612 (28)	
76-100th percentile	875 (27)	302 (28)	573 (26)	
Comorbidities				
Smoking	1123 (34)	352 (32)	771 (35)	0.13
Dyslipidemia	1931 (59)	633 (58)	1298 (59)	0.68
Hypertension	2796 (85)	913 (84)	1883 (85)	0.24
Diabetes mellitus	1092 (33)	279 (26)	813 (37)	**<0.001**
Previous myocardial infarction	390 (12)	112 (10)	278 (13)	0.05
Previous CABG	502 (15)	191 (18)	311 (14)	**0.01**
Congestive heart failure	1236 (38)	414 (38)	822 (37)	0.68
Valvular disease	680 (21)	288 (26)	392 (18)	**<0.001**
Previous cerebrovascular disease	972 (30)	319 (29)	653 (30)	0.85
Peripheral vascular disease	355 (11)	122 (11)	233 (11)	0.58
Renal disease	709 (22)	244 (22)	465 (21)	0.39
Chronic pulmonary disease	695 (21)	214 (20)	481 (22)	0.15
Obesity	495 (15)	85 (7.8)	410 (19)	**<0.001**
Peptic ulcer disease	41 (1.2)	11 (1.0)	30 (1.4)	0.39
Dementia	87 (2.6)	54 (4.9)	33 (1.5)	**<0.001**
Rheumatic disease	97 (2.9)	26 (2.4)	71 (6.5)	0.18
Liver disease	87 (2.6)	14 (1.3)	73 (3.3)	**0.001**
Hypothyroidism	542 (16)	215 (20)	327 (15)	**<0.001**
Charlson Comorbidity Index	2.2±1.9	2.1±1.8	2.3±1.9	**0.02**
0	546 (17)	202 (19)	344 (16)	0.15
1	895 (27)	298 (27)	597 (27)	
2	670 (20)	216 (20)	454 (20)	
≥3	1183 (36)	373 (34)	810 (37)	
Elixhauser Comorbidity Score	9.7±5.8	9.9±5.6	9.7±5.9	0.29
≤0	37 (1.1)	<10 (0.6)	30 (1.4)	0.22
1-5	1189 (36)	387 (36)	802 (36)	
6-10	672 (21)	218 (20)	454 (21)	
≥11	1396 (42)	477 (44)	919 (42)	
Hospital Frailty Risk Score	1.5 (0-3.4)	1.6 (0.4-3.7)	1.5 (0-3.3)	**0.04**

<5 (Low)	2841 (86)	927 (85)	1914 (87)	
5-15 (Intermediate)	440 (13)	156 (14)	284 (13)	0.30
>15 (High)	13 (0.4)	<10 (0.6)	<10 (0.3)	
$CHADS_2$ score	2.7±1.3	3.1±1.2	2.6±1.3	**<0.001**
≥2	2772 (85)	1007 (93)	1765 (80)	**<0.001**
CHA_2DS_2-VASc score	4.2±1.5	4.7±1.4	4.1±1.5	**<0.001**
≥2	3238 (98)	1089 (100)	2149 (98)	**<0.001**
Year of procedure				
2015 (October-December)	114 (3.5)	30 (2.8)	84 (3.8)	
2016 (January-December)	1017 (31)	340 (31)	677 (31)	0.30
2017 (January-December)	2163 (66)	719 (66)	1444 (66)	
In-hospital MAE	153 (4.6)	56 (5.1)	97 (4.4)	0.34
Bleeding complications	19 (0.6)	<10 (0.7)	11 (0.5)	0.40
Cardiac complications	55 (1.7)	21 (1.9)	34 (1.5)	0.42
Vascular complications	16 (0.5)	<10 (0.5)	10 (0.4)	0.70
Stroke	14 (0.4)	<10 (0.6)	<10 (0.4)	0.43
Acute kidney injury	74 (2.2)	23 (2.1)	51 (2.3)	0.71
Length of stay (days)	1 (1-1)	1 (1-1)	1 (1-1)	0.15
Length of stay (days, range)	0-33	0-27	0-33	---
≤1 day	2805 (85)	911 (84)	1894 (86)	0.09
>1 day	489 (15)	178 (16)	311 (14)	
Index admission cost[§], USD	24,143 (18,540-30,232)	24,085 (18,778-29,674)	24,172 (18,424-30,477)	0.50

Values are expressed as mean ± standard deviation, median (interquartile range) or % unless otherwise noted. Exact counts (n) for variables with <10 patients are not detailed as per the Healthcare Cost and Utilization Project data use agreement. [#]Adjusted p-values for each variable were computed from adjusting sampling design by discharge-level weights, cluster and strata. *Race was missing in 3.7%. **Type of admission was missing in 0.4%. ***Median household income was missing in 1.6%. [§]Index admission cost was missing 0.3%. CABG: coronary artery bypass surgery. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack, Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category. MAE: major adverse event. USD: United States dollar.

Table 4.2: Baseline characteristics of the study population according to the occurrence of in-hospital MAE

Patients characteristics	≥80 years (n=1089)			<80 years (n=2205)				
	With in-hospital MAE n=56	Without in-hospital MAE n=1033	Adjusted P-value[#]	With in-hospital MAE n=97	Without in-hospital MAE n=2108	Adjusted P-value[#]	Adjusted P-value[¶]	Adjusted P-value[¥]
Mean age (years)	83.9±2.7	84.1±3.0	0.64	71.5±6.5	71.5±6.5	0.97	**<0.001**	**<0.001**
Women	32 (57)	435 (42)	**0.03**	41 (42)	805 (38)	0.42	0.57	**0.03**
Race*								
White	47 (84)	877 (88)	0.32	74 (80)	1740 (86)		0.53	**0.04**
Non-white	<10 (16)	115 (12)		19 (20)	291 (14)	0.10		
Median household income**								
0-25th percentile	<10 (15)	182 (18)	0.28	19 (21)	433 (21)	0.75	0.19	0.20
26-50th percentile	16 (30)	252 (25)		19 (21)	516 (25)			
51-75th percentile	20 (37)	294 (29)		26 (28)	586 (28)			
76-100th percentile	10 (18)	292 (28)		28 (30)	545 (26)			
Comorbidities								
Smoking	11 (20)	341 (33)	0.04	32 (33)	739 (35)	0.67	0.08	0.26
Dyslipidemia	31 (55)	602 (58)	0.67	64 (66)	1234 (59)	0.14	0.20	0.89
Hypertension	43 (77)	870 (84)	0.14	86 (89)	1797 (85)	0.35	**0.04**	0.45
Diabetes mellitus	16 (29)	263 (25)	0.60	39 (40)	774 (37)	0.48	0.16	**<0.001**
Previous myocardial infarction	<10 (13)	105 (10)	0.58	16 (16)	262 (12)	0.24	0.50	0.06
Previous CABG	11 (20)	180 (17)	0.67	13 (13)	298 (14)	0.84	0.31	**0.02**
Congestive heart failure	30 (54)	384 (37)	**0.01**	47 (48)	775 (37)	**0.02**	0.54	0.83
Valvular disease	17 (30)	271 (26)	0.50	17 (18)	375 (18)	0.95	0.06	**<0.001**
Previous cerebrovascular disease	15 (27)	304 (29)	0.67	20 (21)	633 (30)	0.05	0.36	0.73
Peripheral vascular disease	11 (20)	111 (11)	**0.04**	16 (16)	217 (10)	**0.05**	0.62	0.70
Renal disease	15 (27)	229 (22)	0.42	35 (36)	430 (20)	**<0.001**	0.21	0.25
Chronic pulmonary disease	16 (29)	198 (19)	0.08	16 (16)	465 (22)	0.20	0.07	0.06
Obesity	<10 (14)	77 (7.5)	0.07	19 (20)	391 (19)	0.80	0.42	**<0.001**
Peptic ulcer disease	<10 (1.8)	10 (1.0)	0.55	<10 (1.0)	29 (1.4)	0.77	0.69	0.33
Dementia	<10 (13)	47 (4.5)	**0.01**	<10 (2.1)	31 (1.5)	0.64	**0.01**	**<0.001**
Rheumatic disease	<10 (1.8)	25 (2.4)	0.76	<10 (4.1)	67 (3.2)	0.61	0.43	0.23
Liver disease	<10 (0)	14 (1.3)	0.38	<10 (1.0)	72 (3.4)	0.20	0.45	**<0.001**
Hypothyroidism	11 (20)	204 (20)	0.98	26 (20)	301 (30)	0.12	0.87	**<0.001**

Charlson Comorbidity Index	2.7±2.0	2.1±1.8	**0.02**	2.7±2.0	2.3±1.9	**0.04**	0.85	**0.01**
0	<10 (14)	194 (19)		10 (10)	334 (16)			
1	12 (22)	286 (28)	0.16	23 (24)	574 (27)	0.23	0.80	0.15
2	<10 (16)	207 (20)		20 (21)	434 (21)			
≥3	27 (48)	346 (33)		44 (45)	766 (36)			
Elixhauser Comorbidity Score	11.1±5.3	9.8±5.6	0.09	11.3±6.2	9.6±5.9	**0.01**	0.84	0.29
≤0	0 (0)	<10 (0.7)		<10 (2.1)	28 (1.3)			
1-5	11 (20)	376 (36)	0.06	23 (24)	779 (37)	**0.04**	0.48	0.27
6-10	16 (28)	202 (21)		20 (21)	434 (21)			
≥11	29 (52)	448 (43)		52 (53)	867 (41)			
Hospital Frailty Risk score	3.0 (1.4-5.8)	1.5 (0.4-3.6)	**0.01**	3.3 (1.6-5.4)	1.5 (0-3.2)	**<0.001**	0.44	**0.05**
<5 (Low)	39 (70)	888 (86)		67 (69)	1847 (88)			
5-15 (Intermediate)	14 (25)	142 (14)	**<0.001**	29 (30)	255 (12)	**<0.001**	0.21	0.42
>15 (High)	<10 (5.3)	<10 (0.3)		<10 (1.0)	<10 (0.3)			
$CHADS_2$ (continuous)	3.1±1.3	3.0±1.2	0.70	2.6±1.2	2.6±1.3	0.91	**0.01**	**<0.001**
$CHADS_2$ (categorical)								
≥2	48 (86)	959 (93)	0.05	80 (82)	1685 (80)	0.54	0.61	
CHA_2DS_2-VASc (continuous)	4.9±1.6	4.7±1.4	0.10	4.2±1.6	4.1±1.5	0.38	**0.003**	**<0.001**
CHA_2DS_2-VASc (categorical)								
≥2	56 (100)	1033 (100)	**…**	94 (97)	2055 (97)	0.72	0.19	
Length of stay (days)	2 (1-5)	1 (1-1)	**<0.001**	3 (1-6)	1 (1-1)	**<0.001**	0.18	0.11
≤1 day	18 (32)	893 (86)	**<0.001**	25 (26)	1869 (89)	**<0.001**	0.39	0.07
>1 day	38 (68)	140 (14)		72 (74)	239 (11)			
Index admission cost[§], USD	32,671 (21,342-38,234)	23,939 (18,701-28,949)	**<0.001**	33,014 (25,888-39,330)	23,911 (18,343-30,112)	**<0.001**	0.35	0.64

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%) unless otherwise noted. MAE: major adverse event. Exact counts (n) for variables with <10 patients are not detailed as per the Healthcare Cost and Utilization Project data use agreement. CABG: coronary artery bypass surgery, USD: United States dollar. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke or transient ischemic attack, Vascular disease (including previous myocardial infarction), Age 65-74 years, Sex category**.** *Race was missing 3.8% in ≥80 years cohort and 3.7% in <80 years cohort. **Median household income was missing 1.4% in ≥80 years cohort and 1.5% in <80 years cohort. [§]Index admission cost was missing 0.2% in ≥80 years cohort and 0.4% in <80 years cohort. [#]Adjusted P-values for each variable were computed from adjusting sampling design by discharge-level weights, cluster and strata. Differences between ≥80 years and <80 years with ¶ and without ¥ in-hospital MAE.

Figure 4.1: Temporal trends in left atrial appendage closure procedures performed quarterly and in-hospital complications from 2015-2017 according to age ≥80 years and <80 years.

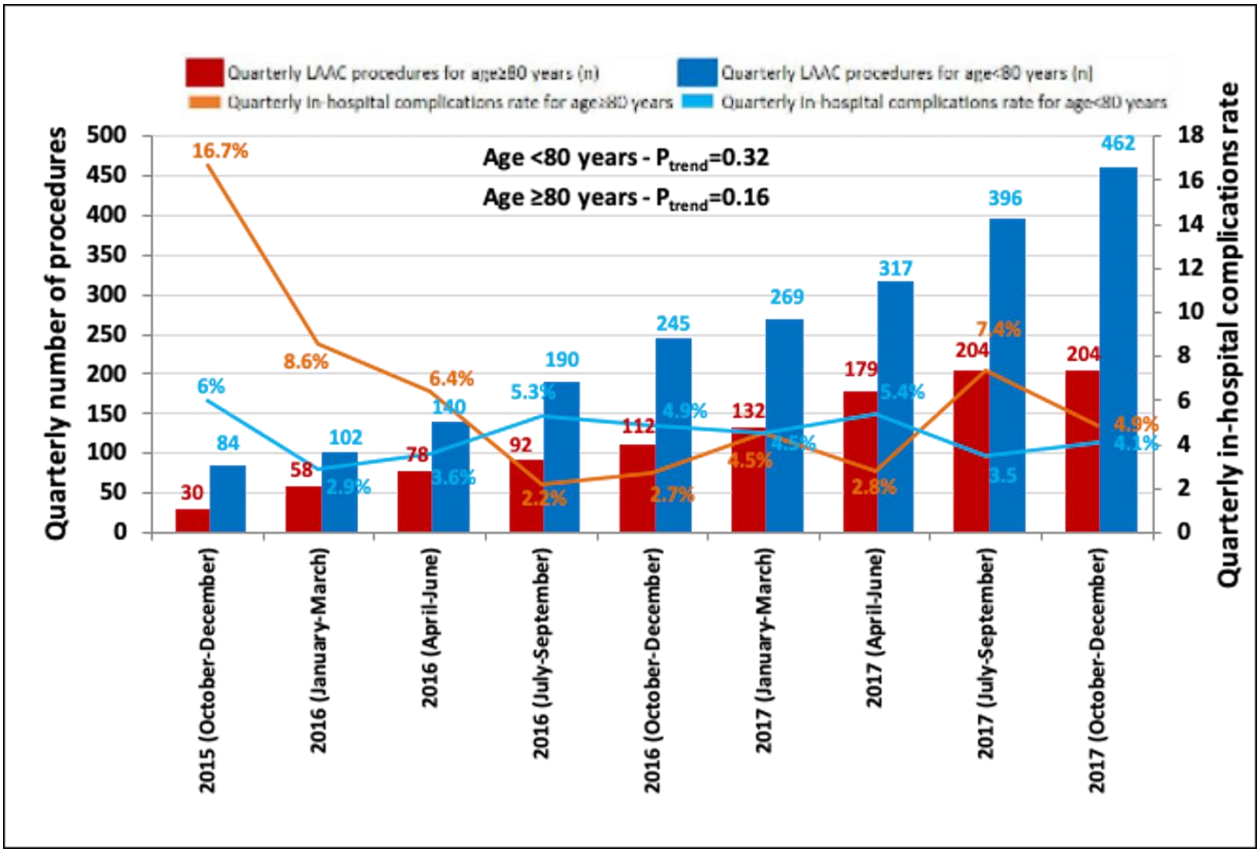


Figure 4.2: Restricted cubic splines showing the proportion of patients according to the trend of Charlson Comorbidity Index, Elixhauser Comorbidity Score and Hospital Frailty Risk Score and its association with the probability of in-hospital major adverse events.

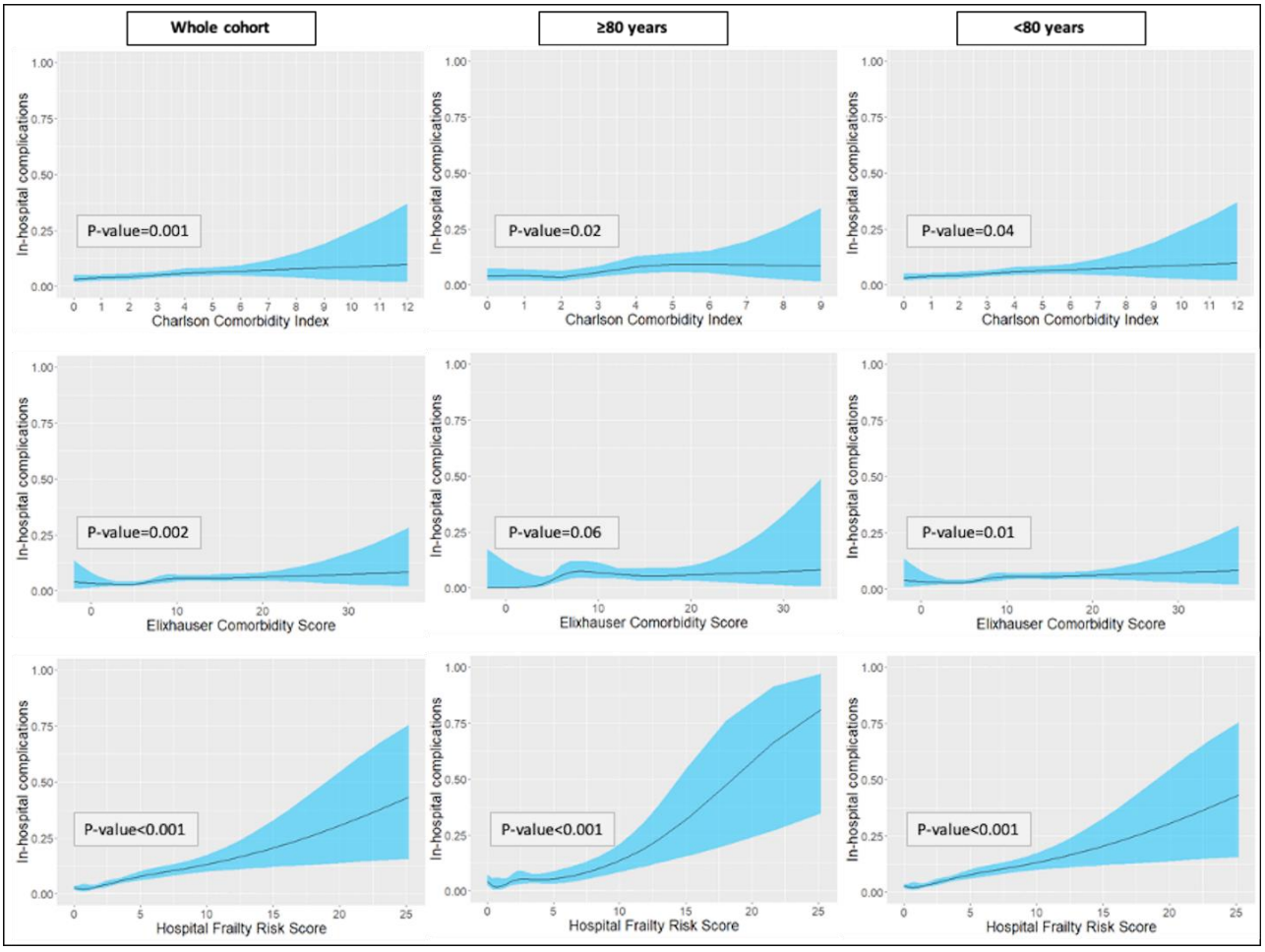
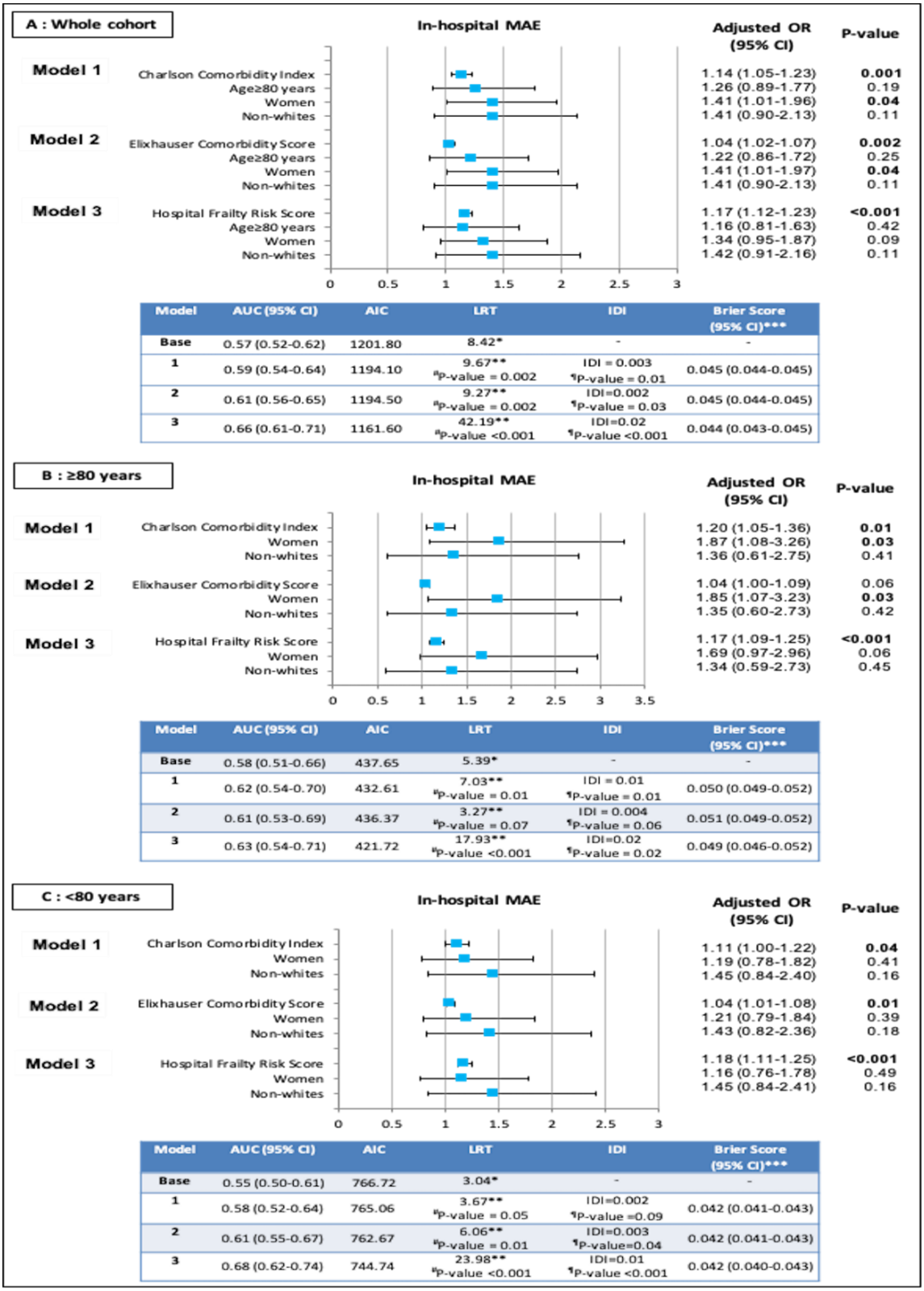
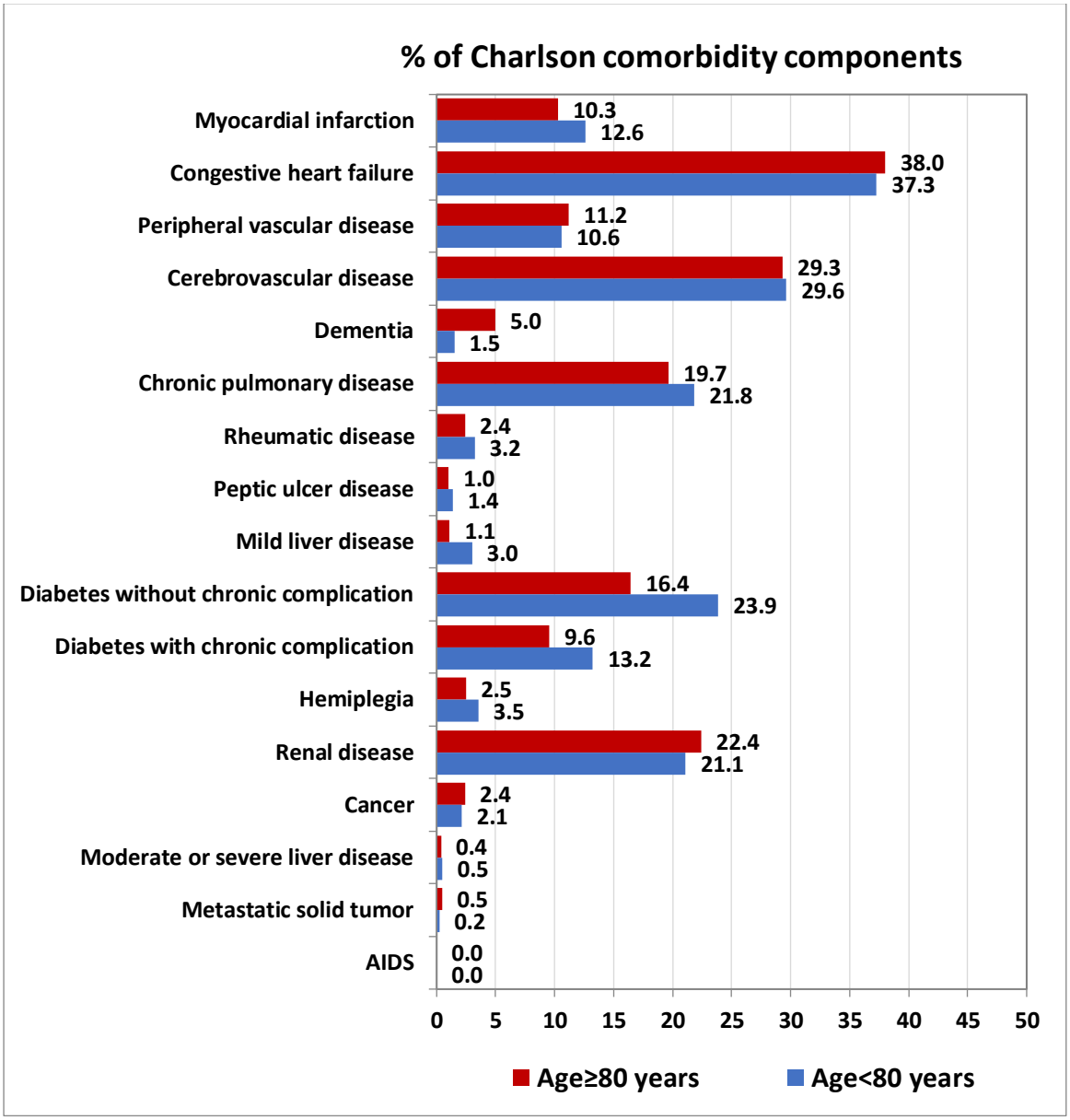


Figure 4.3: Multivariable logistic regression analyses of factors associated with in-hospital major adverse events



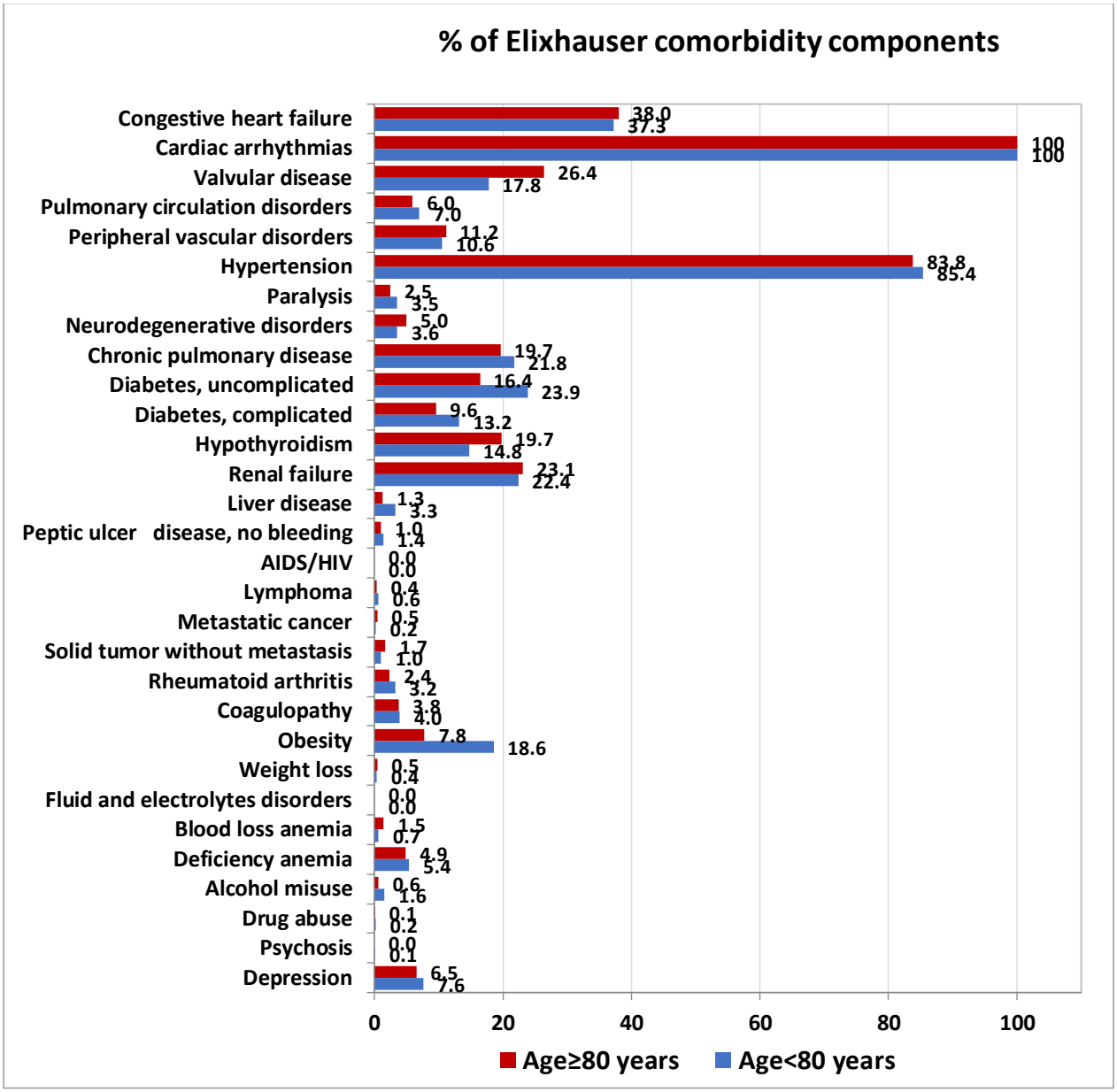
MAE: major adverse events. aOR: adjusted odds ratio. CI: confidence interval. AUC: area under receiver operating curve. LRT: Likelihood ratio test (higher values indicate better performance of the model). AIC: Akaike information criterion (lower values indicate better fit of the model). IDI: Integrated Discrimination Improvement. Base model was adjusted by age, sex and race. Models 1, 2 and 3 were adjusted by age, sex, race and Charlson-weighted score, age, sex, race and Elixhauser-weighted score and age, sex, race and Hospital Frailty Risk Score, respectively. For individuals aged ≥80 years and <80 years, age was not adjusted. For continuous variables, the aOR are per unit of increase in each of the predictive factors. *LRT value against the null model. **LRT value against the base model. [#]P-value against the base model. [¶]P-value against the base model. ***Lower values (close to 0) indicate better calibration of the model. Blue squares with whiskers denote the OR and its CI of in-hospital MAE.

Supplementary Figure 4.1: Proportion of components in Charlson Comorbidity Index.



AIDS: acquired immune deficiency syndrome.

Supplementary Figure 4.2: Proportion of components in Elixhauser Comorbidity Score.



AIDS: acquired immune deficiency syndrome.

Chapter 5

Study Limitations, conclusion and future research

5.1. Study Limitations

The research the lead this thesis presents several limitations. The main limitation of this thesis lies in its observational nature. Secondly, the studies based on an administrative database (NIS), coding error may have occurred during data collection. Third, NIS database does not contain information on medication and laboratories. Consequently, the effect of unmeasured variables (confounders) could not eliminate. Fourth, in-hospital adverse outcomes were identified using ICD-10-CM codes, the severity of specific outcomes of interest may not have been accurately tracked. Fifth, the use of CCI and ECS have limitations because those scores were not developed to predict adverse outcomes in the setting of LAAC. Although, these scores may help determine the risk stratification for clinical decision-making, but a development of valid score is necessary focusing only LAAC. Furthermore, information about the duration of chronic comorbid conditions was not available and this could be an effect modifier which needs to be considered when interpreting these results. Fifth, operator experience with LAAC was not considered during analysis due to a lack of information in NIS database. Sixth, there is a lack of data regarding periprocedural anticoagulation therapy, which might have had an impact on reported outcomes such as bleeding or cerebrovascular accidents. Furthermore, post-interventional and discharge medication (i.e. oral anticoagulants with or without concomitant antiplatelets) management was not available. Finally, the study is limited to in-hospital outcomes, hence, we are unable to provide the impact of comorbid conditions on long-term follow-up, or the prevention of thromboembolism or hemorrhagic events by the LAAC.

5.2. Conclusion

Patients who underwent LAAC presented multiple comorbid conditions and were at risk of in-hospital complications. We found association between comorbidity burden as assessed by CCI, ECS and CHA_2DS_2-VASc scores and in-hospital adverse events. Notably, women were more vulnerable to in-hospital complications compared with men and comorbidities scores were associated with adverse outcomes for women. Importantly, rates of in-hospital complication were similar in patients ≥80 years and <80 years. In this regard, increase in HFRS appears to better predict the risk of in-hospital complications in patients undergoing LAAC. The results of this thesis work may contribute with a better understanding in risk stratification as well as in clinical decision making for patients undergoing LAAC.

5.3. Future Research

The studies of this master's thesis highlight important information about the impact of pre-procedural comorbidities on in-hospital adverse outcomes following LAAC. Because the data source was restricted only to the NIS database, further research is needed to adopting risk minimization strategies for AF patients undergoing LAAC and using other sources of big data. Due to the nature of NIS dataset, our studies did not include a time series analysis (i.e, survival analysis) after discharge and some adverse events may occur after discharge and still be associated to burden of comorbidities. Assessment of complications in follow-up is necessary to investigate long-term outcome after LAAC. Therefore, future research would need to explore for predictors, causes and clinical impact of early (30-day) readmissions as important quality indicator for institutional and healthcare systems as well as late (30-day to 12-month) readmissions. Further study should be focusing on the correction of modifiable factors before a LAAC. For instance, red blood cell

transfusions for the correction anemia before the LAAC procedure and need to establish an appropriate policy for modifiable risk factors. Finally, future studies should assess the long-term impact of comorbidities and frailty on long-term outcomes, including i.e. five-year mortality and stroke, major bleeding and other complications.

Appendix A: Charlson Comorbidity Index and ICD-10-CM codes

Comorbidity	Points	ICD 10-CM codes
Myocardial infarction	1	I25.2
Congestive heart failure	1	I09.81, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x
Peripheral vascular disease	1	I70.x, I71.x, I72.x, I73.1, I73.8, I73.9, I77.1, I77.7, I79.0, I79.1, I79.8, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	1	I69.x, Z86.73
Dementia	1	F01.5, F02.8, F03.9, G30.x, G31.1, G31.8, G31.9
Chronic pulmonary disease	1	I27.8, I27.9, J40.x - J47.x, J60.x - J67.x, J68.4, J70.1, J70.3, J84, J96.1
Rheumatic disease	1	L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0 - M31.3, M32.x - M35.x, M45.x, M46.5, M46.1, M46.8, M46.9, M48.8, M49.8
Peptic ulcer disease	1	K25.5, K25.7, K25.9, K26.5, K26.7, K26.9, K27.5, K27.7, K27.9, K28.5, K28.7, K28.9
Mild liver disease	1	B18.x, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73.x, K74.x, K76.0, K76.0, K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complication	1	E08.9, E09.9, E10.9, E11.9, E13.9
Diabetes with chronic complication	2	E08.2-E08.8, E09.x, E10.2 - E10.8, E11.2 - E11.8, E12.2 - E12.8, E13.2 - E13.8
Hemiplegia	2	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0 - G83.5, G83.8, G83.9, I69.x, R53.2
Renal disease	2	I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0 - Z49.2
Cancer	2	C00.x - C26.x, C30.x - C34.x, C37.x - C41.x, C43.x, C45.x - C58.x, C60.x - C76.x, C81.x - C85.x, C88.x, C90.x - C96.x
Moderate or severe liver disease	3	I85.0, I86.4, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumor	6	C77.x - C80.x, R18.0
AIDS	6	B20

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification. AIDS: acquired immune deficiency syndrome.

Appendix B: Elixhauser Classification System and ICD-10-CM codes

Comorbidity	Points	ICD-10-CM codes
Congestive heart failure	7	I09.81, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x
Cardiac arrhythmias	5	I44.1 - I44.3, I45.6, I45.9, I47.x - I49.x, R00.0, R00.1, R00.8, Z95.0
Valvular disease	-1	A52.0, I05.x - I08.x, I09.1, I09.8, I34.x - I39.x, Q23.0 - Q23.3, Z95.2 - Z95.4
Pulmonary circulation disorders	4	I26.x, I27.x, I28.0, I28.8, I28.9
Peripheral vascular disorders	2	I70.x, I71.x, I72.x, I73.1, I73.8, I73.9, I77.1, I77.7, I79.0, I79.1, I79.8, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Hypertension	0	I10.x, I11.x - I13.x, I15.x
Paralysis	7	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0 - G83.5, G83.8, G83.9, I69.x, R53.2
Neurodegenerative disorders	6	E75.0, E75.1, E75.2, E75.4, F84.2, G10.x - G13.x, G20.x - G21.x, G24.0, G24.2, G24.8, G25.4, G25.5, G30.0, G31.0, G31.1, G31.2, G31.8, G31.9, G32.8, G35.x - G37.x, G80.3
Chronic pulmonary disease	3	I27.8, I27.9, J40.x - J47.x, J60.x - J67.x, J68.4, J70.1, J70.3, J84, J96.1
Diabetes, uncomplicated	0	E08.9, E09.9, E10.9, E11.9, E13.9
Diabetes, complicated	0	E08.2-E08.8, E09.x, E10.2 - E10.8, E11.2 - E11.8, E12.2 - E12.8, E13.2 - E13.8
Hypothyroidism	0	E00.x - E03.x
Renal failure	5	I12.0, I13.1, N18.x, N25.0, Z49.0, Z49.3, Z91.1, Z99.2
Liver disease	11	B18.x, I85.x, K70.x, K71.1, K71.3 - K71.5, K71.7, K72.x - K74.x, K75.4, K75.8, K76.0, K76.2 - K76.9, Z94.4
Peptic ulcer disease, no bleeding	0	K25.5, K25.7, K25.9, K26.5, K26.7, K26.9, K27.5, K27.7, K27.9, K28.5, K28.7, K28.9
AIDS/HIV	0	B20
Lymphoma	9	C81.x - C86.x, C88.x, C90.0, C90.2, C90.3, C96.x, D47.Z9
Metastatic cancer	12	C77.x - C80.x, R18.0
Solid tumor without metastasis	4	C00.x - C26.x, C30.x - C34.x, C37.x - C41.x, C43.x, C45.x - C58.x, C60.x - C76.x, D03.1-D03.9, E31.2
Rheumatoid arthritis/collagen, vascular disease	0	L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0 - M31.3, M32.x - M35.x, M45.x, M46.5, M46.1, M46.8, M46.9, M48.8, M49.8
Coagulopathy	3	D66 - D68.x, D69.1, D69.3 - D69.6
Obesity	-4	E66.x, Z68.3, Z68.4, Z68.5
Weight loss	6	E40.x - E46.x, R63.4, R63.6
Fluid and electrolytes disorders	5	E22.2
Blood loss anemia	-2	D50.0
Deficiency anemia	-2	D501, D50.8, D50.9, D51.x - D53.x, D63.1, D63.8
Alcohol misuse	0	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z71.4
Drug abuse	-7	F11.x - F16.x, F18.x, F19.x, Z71.5

Psychosis	0	F20.x, F22.x - F25.x, F28.x, F29.x, F30.1, F30.2, F31.2, F31.6, F44.8
Depression	-3	F20.4, F31.3 - F31.5, F32.x, F33.x, F34.1, F41.2, F43.2

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification. AIDS/HIV: acquired immune deficiency syndrome and human immunodeficiency virus infection.

Appendix C: Hospital Frailty Risk Score and ICD-10-CM codes

ICD10 Codes	Description	Points
F00	Dementia in Alzheimer's disease	7.1
G81	Hemiplegia	4.4
G30	Alzheimer's disease	4.0
I69	Sequelae of cerebrovascular disease	3.7
R29	Other symptoms and signs involving the nervous and musculoskeletal systems	3.6
N39	Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	3.2
F05	Delirium, not induced by alcohol and other psychoactive substances	3.2
W19	Unspecified fall	3.2
S00	Superficial injury of head	3.2
R31	Unspecified hematuria	3.0
B96	Other bacterial agents as the cause of diseases classified to other chapters	2.9
R41	Other symptoms and signs involving cognitive functions and awareness	2.7
R26	Abnormalities of gait and mobility	2.6
I67	Other cerebrovascular diseases	2.6
R56	Convulsions, not elsewhere classified	2.6
R40	Somnolence, stupor and coma	2.5
T83	Complications of genitourinary prosthetic devices, implants and grafts	2.4
S06	Intracranial injury	2.4
S42	Fracture of shoulder and upper arm	2.3
E87	Other disorders of fluid, electrolyte and acid-base balance	2.3
M25	Other joint disorders, not elsewhere classified	2.3
E86	Volume depletion	2.3
R54	Senility	2.2
Z50	Care involving use of rehabilitation procedures	2.1
F03	Unspecified dementia	2.1
W18	Other fall on same level	2.1
Z75	Problems related to medical facilities and other health care	2.0
F01	Vascular dementia	2.0
S80	Superficial injury of lower leg	2.0
L03	Cellulitis	2.0
H54	Blindness and low vision	1.9
E53	Deficiency of other B group vitamins	1.9
Z60	Problems related to social environment	1.8
G20	Parkinson's disease	1.8
R55	Syncope and collapse	1.8
S22	Fracture of rib(s), sternum and thoracic spine	1.8
K59	Other functional intestinal disorders	1.8
N17	Acute renal failure	1.8
L89	Decubitus ulcer	1.7

Z22	Carrier of infectious disease	1.7
B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	1.7
L97	Ulcer of lower limb, not elsewhere classified	1.6
R44	Other symptoms and signs involving general sensations and perceptions	1.6
K26	Duodenal ulcer	1.6
I95	Hypotension	1.6
N19	Unspecified renal failure	1.6
A41	Other septicemia	1.6
Z87	Personal history of other diseases and conditions	1.5
J96	Respiratory failure, not elsewhere classified	1.5
X59	Exposure to unspecified factor	1.5
M19	Other arthrosis	1.5
G40	Epilepsy	1.5
M81	Osteoporosis without pathological fracture	1.4
S72	Fracture of femur	1.4
S32	Fracture of lumbar spine and pelvis	1.4
E16	Other disorders of pancreatic internal secretion	1.4
R94	Abnormal results of function studies	1.4
N18	Chronic renal failure	1.4
R33	Retention of urine	1.3
R69	Unknown and unspecified causes of morbidity	1.3
N28	Other disorders of kidney and ureter, not elsewhere classified	1.3
R32	Unspecified urinary incontinence	1.2
G31	Other degenerative diseases of nervous system, not elsewhere classified	1.2
Y95	Nosocomial condition	1.2
S09	Other and unspecified injuries of head	1.2
R45	Symptoms and signs involving emotional state	1.2
G45	Transient cerebral ischemic attacks and related syndromes	1.2
Z74	Problems related to care-provider dependency	1.1
M79	Other soft tissue disorders, not elsewhere classified	1.1
W06	Fall involving bed	1.1
S01	Open wound of head	1.1
A04	Other bacterial intestinal infections	1.1
A09	Diarrhea and gastroenteritis of presumed infectious origin	1.1
J18	Pneumonia, organism unspecified	1.1
J69	Pneumonitis due to solids and liquids	1.0
R47	Speech disturbances, not elsewhere classified	1.0
E55	Vitamin D deficiency	1.0
Z93	Artificial opening status	1.0
R02	Gangrene, not elsewhere classified	1.0
R63	Symptoms and signs concerning food and fluid intake	0.9
H91	Other hearing loss	0.9
W10	Fall on and from stairs and steps	0.9
W01	Fall on same level from slipping, tripping and stumbling	0.9

E05	Thyrotoxicosis [hyperthyroidism]	0.9
M41	Scoliosis	0.9
R13	Dysphagia	0.8
Z99	Dependence on enabling machines and devices	0.8
U80	Agent resistant to penicillin and related antibiotics	0.8
M80	Osteoporosis with pathological fracture	0.8
K92	Other diseases of digestive system	0.8
I63	Cerebral Infarction	0.8
N20	Calculus of kidney and ureter	0.7
F10	Mental and behavioral disorders due to use of alcohol	0.7
Y84	Other medical procedures as the cause of abnormal reaction of the patient	0.7
R00	Abnormalities of heartbeat	0.7
J22	Unspecified acute lower respiratory infection	0.7
Z73	Problems related to life-management difficulty	0.6
R79	Other abnormal findings of blood chemistry	0.6
Z91	Personal history of risk-factors, not elsewhere classified	0.5
S51	Open wound of forearm	0.5
F32	Depressive episode	0.5
M48	Spinal stenosis	0.5
E83	Disorders of mineral metabolism	0.4
M15	Polyarthrosis	0.4
D64	Other anemias	0.4
L08	Other local infections of skin and subcutaneous tissue	0.4
R11	Nausea and vomiting	0.3
K52	Other noninfective gastroenteritis and colitis	0.3
R50	Fever of unknown origin	0.1

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

Appendix D: ICD-10-CM codes for in-hospital adverse events

Adverse Events	ICD-10-CM codes
Bleeding complications	
Post procedural hemorrhage	I97.610, I97.618, I97.620, I97.638, J95.830, K91.841, K91.871
Cardiac complications	
Iatrogenic cardiac complications	I97.790, I97.88, I97.89
Pericardial complications	
Hemopericardium	I31.2
Cardiac tamponade	I31.4
Pericardiocentesis	0W9D30Z, 0W9D3ZZ
Complete heart block	0JH604Z, 0JH606Z, 0JH636Z
Postprocedural cardiogenic shock	T81.11XA
Requiring open heart surgery	02Q50ZZ
Cardiac arrest	I46.9
Acute myocardial infarction	I21.4
Post-procedural stroke or transient ischemic attack	I63.50, I63.9, G45.9
Vascular complications	
Accidental puncture	I97.51
Other vascular complications	T81.718A, T81.72XA
Vascular complications requiring surgery	04QK0ZZ
Acute kidney injury	N17.0, N17.9, N99.0, R34

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

Appendix E: Data use agreement for the Nationwide Databases from the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality

HCUP-CDOW-OrderID: 092518006SANJOYSHUB19541_NRD.NIS Applicant: Shubrandu Sanjoy

DATA USE AGREEMENT for the Nationwide Databases from the Healthcare Cost and Utilization Project Agency for Healthcare Research and Quality

This Data Use Agreement ("Agreement") governs the disclosure and use of data in the HCUP Nationwide Databases from the Healthcare Cost and Utilization Project (HCUP) which are maintained by the Center for Delivery, Organization, and Markets (CDOM) within the Agency for Healthcare Research and Quality (AHRQ). The HCUP Nationwide databases include the National (Nationwide) Inpatient Sample (NIS), Kids' Inpatient Database (KID), Nationwide Emergency Department Sample (NEDS), and Nationwide Readmissions Database (NRD). Any person ("the data recipient") seeking permission from AHRQ to access HCUP Nationwide Databases must read and accept this Agreement electronically, and complete the online Data Use Agreement Training Course at www.hcup-us.ahrq.gov, as a precondition to the granting of such permission.

Section 944(c) of the Public Health Service Act (42 U.S.C. 299c-3(c)) ("the AHRQ Confidentiality Statute"), requires that data collected by AHRQ that identify individuals or establishments be used only for the purpose for which they were supplied. Pursuant to this Agreement, data released to AHRQ for the HCUP Databases are subject to the data standards and protections established by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (P.L. 104-191) and implementing regulations ("the Privacy Rule"). Accordingly, HCUP Databases may only be released in "limited data set" form, as that term is defined by the Privacy Rule, 45 C.F.R. § 164.514(e). HCUP data may only be used by the data recipient for research which may include analysis and aggregate statistical reporting. AHRQ classifies HCUP data as protected health information under the HIPAA Privacy Rule, 45 C.F.R. § 160.103. By executing this Agreement, the data recipient understands and affirms that HCUP data may only be used for the prescribed purposes, and consistent with the following standards:

No Identification of Persons–The AHRQ Confidentiality Statute prohibits the use of HCUP data to identify any person (including but not limited to patients, physicians, and other health care providers). The use of HCUP Databases to identify any person constitutes a violation of this Agreement and may constitute a violation of the AHRQ Confidentiality Statute and the HIPAA Privacy Rule. This Agreement prohibits data recipients from releasing, disclosing, publishing, or presenting any individually identifying information obtained under its terms. AHRQ omits from the data set all direct identifiers that are required to be excluded from limited data sets as consistent with the HIPAA Privacy Rule. AHRQ and the data recipient(s) acknowledge that it may be possible for a data recipient, through deliberate technical analysis of the data sets and with outside information, to attempt to ascertain the identity of particular persons. Risk of individual identification of persons is increased when observations (i.e., individual discharge records) in any given cell of tabulated data is ≤ 10. This Agreement expressly prohibits any attempt to identify individuals, including by the use of vulnerability analysis or penetration testing. In addition, methods that could be used to identify individuals directly or indirectly shall not be disclosed, released, or published. Data recipients shall not attempt to contact individuals for any purpose whatsoever, including verifying information supplied in the data set. Any questions about the data must be referred exclusively to AHRQ. By executing this Agreement, the data recipient understands and agrees that actual and considerable harm will ensue if he or she attempts to identify individuals. The data recipient also understands and agrees that actual and considerable harm will ensue if he or she intentionally or negligently discloses, releases, or publishes information that identifies individuals or can be used to identify individuals.

Use of Establishment Identifiers–The AHRQ Confidentiality Statute prohibits the use of HCUP data to identify establishments unless the individual establishment has consented. Permission is obtained from the HCUP data sources (i.e., state data organizations, hospital associations, and data consortia) to use the identification of hospital establishments (when such identification appears in the data sets) for research, analysis, and aggregate statistical reporting. This may include linking institutional information from outside data sets for these purposes.

Such purpose does *not* include the use of information in the data sets concerning individual establishments for commercial or competitive purposes involving those individual establishments, or to determine the rights, benefits, or privileges of establishments. Data recipients are prohibited from identifying establishments directly or by inference in disseminated material. In addition, users of the data are prohibited from contacting establishments for the purpose of verifying information supplied in the data set. Any questions about the data must be referred exclusively to AHRQ. Misuse of identifiable HCUP data about hospitals or any other establishment constitutes a violation of this Agreement and may constitute a violation of the AHRQ Confidentiality Statute.

By checking the Acknowledgment box or accessing or using any part of the HCUP Nationwide databases, data recipients agree to provide the following affirmations concerning HCUP data:

Protection of Individuals

- I will not release or disclose, and will take all necessary and reasonable precautions to prohibit others from releasing or disclosing, any information that directly or indirectly identifies persons. This includes attempts to identify individuals through the use of vulnerability analysis or penetration testing.
- I acknowledge that the release or disclosure of information where the number of observations (i.e., individual discharge records) in any given cell of tabulated data is ≤ 10 can increase the risk for identification of persons. I will consider this risk and avoid publication of a cell containing a value of 1 to 10.
- I will not attempt to link, and will prohibit others from attempting to link, the discharge records of persons in the data set with individually identifiable records from any other source.
- I will not attempt to use and will take all necessary and reasonable precautions to prohibit others from using the data set to contact any persons in the data for any purpose.

Protection of Establishments

- I will not publish or report, through any medium, data that could identify individual establishments directly or by inference.
- When the identities of establishments are not provided in the data sets, I will not attempt to use and will take all necessary and reasonable precautions to prohibit others from using the data set to learn the identity of any establishment.
- I will not use and will take all necessary and reasonable precautions to prohibit others from using the data set concerning individual establishments: (1) for commercial or competitive purposes involving those individual establishments; or (2) to determine the rights, benefits, or privileges of individual establishments.
- I will not contact and will take all necessary and reasonable precautions to prohibit others from contacting establishments identified in the data set to question, verify, or discuss data in the HCUP databases.
- I acknowledge that the HCUP NIS, KID, and NRD may contain data elements from proprietary restricted computer software (e.g., 3M™ APR DRGs) supplied by private vendors to AHRQ for the sole purpose of supporting research and analysis with the HCUP NIS, KID, and NRD. While I may freely use these data elements in my research work using the HCUP NIS, KID, and NRD I agree that I will not use and will prohibit others from using these proprietary data elements for any commercial purpose. In addition, I will enter into a separate agreement with the appropriate organization or firm for the right to use such proprietary data elements for commercial purposes. In particular, I agree not to disassemble, decompile, or otherwise reverse-engineer the proprietary software, and I will prohibit others from doing so.

Limitations on the Disclosure of Data and Safeguards

- I acknowledge and affirm that I am personally responsible for compliance with the terms of this Agreement, to the exclusion of any other party, regardless of such party's role in sponsoring or funding the research that is the subject of this Agreement.

- I will only allow access to HCUP Nationwide data to those who have become authorized users of the HCUP data by signing a copy of this Data Use Agreement and completing the online Data Use Agreement Training Course at www.hcup-us.ahrq.gov. Before granting any individual access to the data set, I will submit the signed data use agreements to the address at the end of this Agreement.

- I will not use or disclose and I will prohibit others from using or disclosing the data set, or any part thereof, except for research, analysis, and aggregate statistical reporting, and only as permitted by this Agreement.

- I will not redistribute HCUP data by posting on any Website or other publicly-accessible online repository.

- I will ensure that the data are kept in a secured environment and that only authorized users will have access to the data.

- I acknowledge and affirm that interpretations, conclusions, and/or opinions that I reach as a result of my analyses of the data sets are my interpretations, conclusions, and/or opinions, and do not constitute the findings, policies, or recommendations of the U.S. Government, the U.S. Department of Health and Human Services, or AHRQ.

- I agree to acknowledge in all reports based on these data that the source of the data is the "National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality." Substitute "Nationwide Inpatient Sample (NIS)" (if using data prior to 2012), "Kids' Inpatient Database (KID)," "Nationwide Emergency Department Sample (NEDS)," or "Nationwide Readmissions Database (NRD)" as appropriate.

- I will indemnify, defend, and hold harmless AHRQ and the data organizations that provide data to AHRQ for HCUP from any or all claims and losses accruing to any person, organizations, or other legal entity as a result of violation of this Agreement. This provision applies only to the extent permitted by Federal and State law.

- I agree to report the violation or apparent violation of any term of this Agreement to AHRQ without unreasonable delay and in no case later than 30 calendar days of becoming aware of the violation or apparent violation.

Terms, Breach, and Compliance

Any violation of the terms of this Agreement shall be grounds for immediate termination of this Agreement. AHRQ shall determine whether a data recipient has violated any term of the Agreement. AHRQ shall determine what actions, if any, are necessary to remedy a violation of this Agreement, and the data recipient(s) shall comply with pertinent instructions from AHRQ. Actions taken by AHRQ may include but not be limited to providing notice of the termination or violation to affected parties and prohibiting data recipient(s) from accessing HCUP data in the future.

In the event AHRQ terminates this Agreement due to a violation, or finds the data recipient(s) to be in violation of this Agreement, AHRQ may direct that the undersigned data recipient(s) immediately return all copies of the HCUP Nationwide Databases to AHRQ or its designee without refund of purchase fees.

Acknowledgment

I understand that this Agreement is requested by the United States Agency for Healthcare Research and Quality to ensure compliance with the AHRQ Confidentiality Statute. Checking the Acknowledgment box or accessing or using any part of the HCUP Nationwide databases indicates that I understand the terms of this Agreement and that I agree to comply with its terms. I understand that a violation of the AHRQ Confidentiality Statute may be subject to a civil penalty of up to $14,140 under 42 U.S.C. 299c-3(d), and that deliberately making a false statement about this or any matter within the jurisdiction of any department or agency of the Federal Government violates 18 U.S.C. § 1001 and is punishable by a fine, up to five years in prison, or both. Violators of this Agreement may also be subject to penalties under state confidentiality statutes that apply to these data for particular states.

Signed: Digitally Acknowledged on Order 19541 09/25/18 Date: 09/25/18

Print or Type Name: Shubrandu Sanjoy

Title:

Organization: Western University

Address: London, Ontario

Address:

City: London State: Ontario ZIP Code: N6A 3K7

Phone: 2269778831 Fax:

E-mail: shubrandu.sanjoy@northsouth.edu

The information above is maintained by AHRQ only for the purpose of enforcement of this Agreement and for notification in the event data errors occur.

Note to Purchaser: Shipment of the requested data product will only be made to the person who executes this Agreement, unless special arrangements that safeguard the data are made with AHRQ or its agent.

Appendix F : Curriculum Vitae

Curriculum Vitae

SHUBRANDU SANJOY

EDUCATION

Degrees

2018.09 – 2020.08 Master of Science, Epidemiology and Biostatistics,
Western University, London, ON, Canada.
Supervisors: Dr. Rodrigo Bagur and Dr. Yun-Hee Choi.

2015.01 - 2016.04 Master of Public Health, Epidemiology
North South University, Bangladesh
Supervisor: Dr. Ahmed Hossain.

2010.01 - 2014.04 Bachelor of Science
Shahjalal University of Science and Technology, Bangladesh

EMPLOYMENT

2018.09 - 2020.08 Graduate Research Assistant
Department of Epidemiology and Biostatistics
Schulich Medicine & Dentistry, Western University
London, ON, Canada.

2019.09 - 2020.04 Proctor
King's University College at Western University
London, ON, Canada.

2016.03 - 2018.08 Lecturer (Epidemiology and Biostatistics)
BRKCN College (affiliated with Shahjalal University of Science and Technology), Bangladesh.

FUNDING AND AWARDS

Western Graduate Research Scholarship (WGRS)
Amount: $10,800 CAD
Lawson Internal Research Fund Studentship Award Fall 2019
Amount: $15,000 CAD
Ontario Student Opportunity Trust Fund Bursary Award
Amount: $3,000 CAD

PUBLICATIONS

1. Bagur, R., Choi, Y. H., Holmes, D. R., Herrmann, H., Terre, J., Alraies, M. C., & **Sanjoy, S. S.** (2020). Comorbidity Burden in Patients Undergoing Left Atrial Appendage Closure. *Journal of the American College of Cardiology*, *75*(11 Supplement 1), 1506.
2. Bagur, R., Solomonica, A., Taleb, H., **Sanjoy, S. S**., Israeli, Z., & Lavi, S. (2020). Postprocedural Radial Artery Compression Time in Chronic Anticoagulated Patients Using Statseal. The Practical-Seal Feasibility Study. *Journal of the American College of Cardiology*, 75(11 Supplement 1), 1525.
3. **Sanjoy, S. S**., Ahsan, G. U., Nabi, H., Joy, Z. F., & Hossain, A. (2017). Occupational factors and low back pain: a cross-sectional study of Bangladeshi female nurses. *BMC research notes*, *10*(1), 173.
4. Irfan, S. D., Faruque, M. O., Islam, M. U., **Sanjoy, S. S**., Afrin, D., & Hossain, A. (2017). Socio-demographic determinants of adult tuberculosis: a matched case-control study in Bangladesh. *American Journal of Infectious Diseases*, 13(3), 32-7.