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Sex Differences in Patient Outcomes Following Surgical Intervention for Acute Type A Aortic Dissection in Armenia

Master of Public Health Integrating Experience Project
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By

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List of abbreviations

AAAD	Acute A type aortic dissection
ACCT	Aortic cross clamp time
AMC	Astghik Medical Center
AoR	Aortic regurgitation
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CPB	Cardiopulmonary bypass
CPR	Cardiopulmonary resuscitation
DHCA	Deep hypothermic circulatory arrest
ICU	Intensive care unit
IMH	Intramural hematoma
IRAD	International Registry of Acute Aortic Dissection
LH	Leipzig - Halifax
LOS	Length of stay
LVEF	Left ventricular ejection fraction
NMMC	Nork Marash Medical Center
PAU	Penetrating aortic ulcer

Abstract

Background: Acute aortic dissection is a life-threatening pathology with a very high risk of mortality if untreated. Surgical treatment of acute A type aortic dissection (AAAD) decreases mortality rates; however, in-hospital mortality risk still remains high. Sex differences in postsurgical outcomes of AAAD are controversial in literature.

Objective: The study was conducted in two tertiary care hospitals in Armenia, at the Nork Marash Medical center (NMMC) and the Astghik Medical Center (AMC). The primary objective of the study was to evaluate differences in in-hospital mortality of AAAD between sexes. Secondary objectives included the evaluation of differences in in-hospital morbidity (complications), differences in patient profiles and disease manifestation of AAAD between sexes as well as investigation of the predictors of in-hospital mortality, changes in patient outcomes over time and the validity of the Leipzig-Halifax (LH) score to predict mortality in Armenian AAAD population.

Methods: We conducted a retrospective cohort study with inclusion of all patients who were admitted to the NMMC and AMC and underwent surgery for AAAD from January 1, 2008 to April 1, 2018. Information from the medical records were extracted and analyzed. To estimate the independent effect of sex on in-hospital mortality and to evaluate the independent predictors of in-hospital mortality we conducted multivariable logistic regression analyses.

Results: Overall, 211 patients were included in the study. The majority were males (76.3%, n = 161). Females were significantly older than males (59.2 ± 10.3 vs. 55.8 ± 9.1, $p = 0.027$). After adjustment for age, LH score and cardiopulmonary bypass (CPB) time sex was not an independent predictor of in-hospital mortality for patients with AAAD (OR = 0.526, 95 % CI: 0.22 to 1.43). LH score and CPB time ≥ 240 minutes were the predictors of in-hospital mortality. Based on adjusted analysis, no difference in in-hospital mortality was observed between 2008-2012 and 2013-2018 time periods. Model discrimination for the LH score assessed by area under the receiver operating curve was fair (AUC ROC = 0.634).

Conclusions: We did not find difference in in-hospital mortality of surgically treated AAAD between males and females in Armenia. Longer CPB time and severity at presentation measured by the LH score were the independent predictors of in-hospital mortality after AAAD surgery. The predictive power of LH score was fair for the Armenian population. It is important to evaluate the long-term outcomes of AAAD in this cohort.

1. Introduction

1.1 Background

Acute aortic syndrome is a life threatening condition, which includes pathologies such as classic aortic dissection, aortic intramural hematoma (IMH) and penetrating aortic ulcer (PAU).[1,2] In the clinical practice we are mostly dealing with the aortic dissection,[1,3] however PAU may progress and become IMH, IMH may become true dissection and the false lumen of the true dissection may thrombose, mimicking IMH.[4] This classification in case of ascending aorta is mostly academic, because they all treated as dissections.[4] Aortic dissection is a tear in the internal lining of the aorta, leading to separation (dissection) of the inner and middle layers of the aortic wall and, causing a false lumen.[5] The main cause of death following dissection if remained undiagnosed and/or untreated is aortic external rupture (hemopericardium and hemothorax).[6,7]

Aortic dissection is a relatively rare disease. Based on autopsy data its prevalence ranges from 0.2% to 0.8%[8] 100-200 less than coronary heart disease (CHD).[9,10] From the 1000 cases admitted to the emergency room with chest or back pain only 3 are diagnosed as aortic dissections.[11] Taking into account the fact of the rarity and understanding the importance of better assessment of etiology, clinical manifestation, imaging findings, management and outcomes of both Type A and Type B acute aortic dissections the International Registry of Acute Aortic Dissection (IRAD) had been established in 1996.[12] In 1996 IRAD included data from twelve referral centers from six countries.[12] Currently, the IRAD database contains information on 6.500 patients from 43 centers worldwide.[13] Studies drawing upon IRAD data report that 62.3% of all patients with dissection ns had acute Type A aortic dissection (AAAD).[12] Another population-based study conducted from Mayo clinic reported that about 85% among all dissections were AAAD.[14]

According to DeBakey classification aortic dissections are divided into Type I, II and III: Type I involves the ascending, arch and descending aorta, Type II involves the ascending aorta and Type III involves the descending aorta.[15] Stanford classifies aortic dissections according to surgery need. Stanford Type A involves the ascending aorta (therefore, includes DeBakey Types I and II), which requires surgical management and Type B involves only the descending part of the aorta (DeBakey Type III) and requires mostly medical management.[16] Aortic dissection is considered acute within the first two weeks following symptom onset and chronic thereafter.[16,17]

The estimated global aortic aneurysms death rate (including dissections) was 2.49/100,000 in 1990, and 2.78/100,000 in 2010. Moreover, males had higher rate of death as compared with females (2.86 vs. 2.12/100,000 in 1990, and 3.40 vs. 2.15/100,000 in 2010).[18] The mortality risk of AAAD without surgery (natural history of the disease) is 50% during the first 48 hours and 80% during the first two weeks, 1-2% per hour if untreated.[19] IRAD data revealed that mortality of AAAD in patients not undergoing surgery because of advance age and comorbidities is 58%.[12] In an IRAD cohort including 464 patients from 1996 to 1998 only 72% of cases underwent surgical managements for AAAD; the surgical mortality was 26% and the in-hospital mortality was 34.9%.[12] Data from 28 centers enrolled in IRAD that included 4428 patients admitted for aortic dissection from 1996 to 2013 reported 90% surgical management rate for AAAD.[20] In this cohort the in-hospital mortality was 24.4% and the surgical mortality was 19.7%.[20] Although still high, this shows declining trends in in-hospital and surgical mortality for AAAD over time.[12,20]

The incidence of acute aortic dissection is considered to be underestimated, because of difficulties in diagnosis.[5] The high clinical suspicion from the professionals about acute aortic event is necessary, because it is a rare disease.[12] Eventually, about 46.8% of patients with AAAD die before reaching to the hospital, which again creates difficulties to precisely report the incidence rate of the disease.[14] A study was conducted in Olmsted County, Minnesota, which included patients from 1980 to 1994 and determined incidence and long-term survival rate of acute aortic dissection revealed that age and gender-adjusted incidence was 3.5/100,000 person-years, from which 85% were contributed to AAAD.[21] Another population-based longitudinal study was conducted in Hungary following 106,500 populations over 27 years (from 1972 to 1998) and analyzing medical, surgical and autopsy records described 2.9/100,000 person-years incidence of aortic dissections.[22] A prospective population-based study following a population of 92,728 people for 10 years from Oxfordshire United Kingdom revealed that incidence of thoracoabdominal aortic dissection was 6/100,000 person-years (59 dissections, from which 37 had type A dissection).[14] This study accounted autopsy cases as well.

Systemic hypertension is a major risk factor for AAAD and is present in about 80% of patients with AAAD.[14,20,23] The risk of aortic dissection is four times higher in individuals with hypertension as compared with individuals with normal blood pressure (21/100,000 patients/years in hypertensives and 5/100,000 patients/years in normotensives).[24] Hypertension HR is 3.37 (95% CI, 1.51 to 7.55). Other important risk factors include aging (HR is 2.3 with 95% CI ranges from 1.57 to 3.36), sex (HR is 1.84 with 95% CI ranges from1.05 to 3.23), smoking status (HR is 1.91 with 95% CI ranges from 1.12 to 3.25).[24] Aortic dilatation, aortitis, pregnancy, chest trauma, iatrogenic causes (cardiac surgery, heart catheterization), drug use are the other risk factors of aortic dissection.[3] Genetic factors such as congenital cardiovascular defects (bicuspid aortic valve and coarctation of the aorta), syndromic conditions (Marfan syndrome, Loeys-Dietz syndrome, Ehlers Danlos syndrome and Turner syndrome) and non-syndromic familial Thoracic aortic dissections (TAD) are another group of the risk factors.[3,20] According to IRAD data 93% of the patients with AAAD manifest with severe, tearing and sharp onset chest or back pain with the chest pain predomination in 85% of the patients. Nineteen percent of the patients present with syncope and 31% - with pulse deficit.[20] Hypotension/shock, neurological deficits, acute renal failure, previous cardiac surgery and age are the predictors of higher mortality in patients with AAAD.[25]

Gender differences in risk factors, management and outcomes of acute aortic dissection have been explored in different studies. Male female ratio of aortic dissection is about 2:1 according to different sources.[3,21–23] A study evaluating gender related differences in acute aortic dissection among 1078 patients from the IRAD found that women were significantly older and were admitted to the hospital later as compared with men.[26] The same study revealed that complications such as altered mental status (coma), hypotension, periaortic hematoma, pleural and pericardial effusion and tamponade were found more frequently in women. The age- and hypertension-adjusted mortality of acute aortic dissection were higher in women, especially in 66-75-year age category as compared with the same age category men. Women patients undergoing surgery for AAAD had higher surgical mortality comparing with men (32% vs. 22%).[26] A retrospective study conducted in Japan among 504 patients undergoing surgery for AAAD described that females were older and had smaller body surface area (BSA) compared to males.[27] However, the study did not find significant differences in operative mortality, postoperative complications, length of stay (LOS) in intensive care unit (ICU), in 5-year mortality and late reoperation rate between sexes. In this study the outcome analysis had not been adjusted for confounders. A single center study conducted in Iran with relatively small number of patients, which performed propensity matching to adjust for confounders (hypertension, diabetes mellitus, smoking, age, prior stroke, history of bicuspid aortic valve and hemoglobin level variables were used to calculate propensity score), found no difference between genders undergoing surgery for AAAD in their early and late outcomes.[28] Another multicenter study conducted in Israel, which enrolled patients from 4 centers, did not reveal difference between males and females in AAAD early and late outcomes (this study used univariate analysis only).[29] Studies are summarized in Appendix 1. Therefore, the findings regarding gender differences in AAAD risk factors and outcomes have not been consistent in the literature.

Predictors of mortality of surgically treated patients for type A aortic dissection have been studied extensively during the last decade. Studies showed that preoperative shock, cardiac tamponade, preoperative malperfusion, advanced age are the independent predictors of mortality in patients after surgery for AAAD.[30–32] Because AAAD is a relatively rare condition, few prognostic tools are currently available in literature to predict operative mortality for AAAD, one of them being the Penn classification based on the preoperative end-organ and/or generalized ischemia.[33,34] Recently, the Leipzig-Halifax (LH) scorecard was developed for the German and Canadian populations and was further validated for the Swedish AAAD population.[35,36] The Penn classification is one of the components of the LH score.

1.2 Situation in Armenia

Armenia had the second highest mortality rate from aortic aneurysms (including dissections) in 2013, which was 7.3/100,000 population.[37] However, no study has focused on aortic dissections in Armenia specifically. The prevalence of hypertension, the main risk factor of acute aortic dissection, was 28.6% in 2016 among the adult Armenian population.[38]

The Nork-Marash Medical Center (NMMC) is one of the biggest Transcaucasian cardiac surgery centers and is located in Yerevan, the capital city of Armenia. The center serves about 14,000 people with heart diseases in the region and performs more than 800 heart surgeries annually.[39] Annually about 25-30 patients with acute aortic dissection undergo ascending aortic repair at NMMC (the only center in Armenia performing surgeries and invasive procedures on the ascending aorta until 2016), classifying it as a high-volume center (more than 13 surgeries annually).[40] Astghik Medical Center (AMC) is a multifunction center, which added a cardiac surgery department in March 2016 and is now a high volume aortic dissection surgery center as well.[41]

1.3 Study rationale

Based on the current literature, gender differences in acute aortic dissection outcomes is controversial. The 2014 European Society of Cardiology (ESC) Guidelines on the diagnosis and treatment of aortic diseases mention a gap in the literature regarding gender-related differences in the management of aortic diseases.[42] This gaps extends to Armenia, where literature regarding aortic dissections is lacking. Therefore, a study evaluating differences in manifestation (baseline clinical characteristics), differences in patient profiles and sex-related differences in outcomes of AAAD over several years of disease management in Armenia would fill an important knowledge gap.

1.4 Study objectives

The primary objective of the study was to:

- Evaluate differences in in-hospital mortality of AAAD between males and females.

The secondary objectives were to:

1. Explore differences in patient profiles and disease manifestation of AAAD between sexes;
2. Evaluate differences in in-hospital morbidity (complications) of AAAD between sexes;

3. Explore the predictors of in-hospital mortality of AAAD;
4. Explore the changes in patient outcomes of AAAD at NMMC and AMC from 2008 to 2018;
5. Evaluate the validity of the LH score to predict mortality in Armenian AAAD population.

2. Methods

2.1 Study design

We conducted a retrospective cohort study to address the study objectives. We included all consecutive patients who were admitted to the NMMC and AMC and underwent surgery for AAAD from January 1 2008 to April 1 2018. We choose this time frame, because medical records in NMMC are available starting from 2008 and at NMMC the high volume of surgeries for AAAD started from 2009.

2.2 Study population

The study target population includes patients with AAAD in Armenia. The study included all patients who had surgery for AAAD after admission to NMMC and AMC from January 1 2008 to April 1 2018. Patients admitted to the centers during the same time period with traumatic dissections and congenital heart diseases such as bicuspid aortic valve and aortic coarctation were excluded.

2.3 Selection of study sample

The NMMC and AMC cardiac surgery departments' adult clinic computerized databases were the source of information for selecting patients who were admitted to these hospitals with AAAD. The electronic database, patients discharge documents and medical records of all these patients were obtained and reviewed for eligibility criteria.

2.4 Study variables

The primary study outcome was in-hospital mortality.[27] Another, secondary outcome was any complication after surgery, a combined variable that included stroke, renal failure, mesenteric ischemia, limb ischemia, reoperation for bleeding and others (Appendix 2). Preoperative independent variables were age, sex, smoking status, hypertension (HT), diabetes mellitus (DM), ischemic heart disease, type of dissection and other comorbidities. Operative and postoperative independent variables were type of the surgery, operation time, aortic cross clamp time, presence or absence of coronary artery bypass grafting and others. All the variables are listed in Appendix 2. Continuous variables were dichotomized using established threshold values. We categorized patients based on cardiopulmonary bypass (CPB) time $\geq$ 240 minutes or less; deep hypothermic circulatory arrest (DHCA) time $\geq$ 59 minutes or less[43]; ventilation time $\geq$ 48 hours or less; and ICU stay $\geq$120 hours or less. These cut-off values were based on past literature that showed that patients with ICU stay for more than 120 hours (prolonged ICU stay) had longer CPB time, and more postoperative complications such as stroke, respiratory failure and renal failure.[44] Patients, who were ventilated longer than 48 hours (prolonged ventilation) had again longer CPB time. Other predictors of prolonged ventilation were previous cardiac surgery and cardiogenic shock.[34,45]

2.4.1 Definitions

We calculated the Leipzig-Halifax (LH) score in accordance with the original studies [35,36]. The LH score is a composite score constructed by addition of scores assigned to each of the following risk factors: 1. Critical preoperative state, 2. Penn class-non Aa ischemia and 3. CAD, where

1. Critical preoperative state is defined as a presence of preoperative inotropic support and/or preoperative mechanical ventilation and/or preoperative cardiopulmonary resuscitation. Patients having any of these preoperative conditions are considered to be in a critical preoperative state, with an allocated score of 10.
2. Penn classification[33,34,43] stratifies patients into four classes based on ischemia type. Penn class Aa patients have no ischemia, Penn class Ab patients have any end organ ischemia (cerebral ischemia, extremity ischemia, renal ischemia, visceral ischemia and spinal ischemia). Penn class Ac includes patients with the shock, cardiac tamponade and myocardial ischemia with ST segment elevation more than 0.1 mV on ECG.[33] Penn class Abc includes patients with both end organ and general ischemia. "Penn class non-Aa" is a composite class with an assigned score of 10 and includes patients from Penn classes Ab, Ac and Abc.
3. History of coronary artery disease is the third variable used in a calculation of LH score and patients with CAD receive 5 points.

The LH cumulative score ranges from 0 to 25, with 5-point increments. Based on the LH cumulative scores, each patient was classified into low, medium and high risk groups where patients with scores <10 were included in the low risk group, patients with 10 – 15 scores were in the medium risk group and those with scores >15 were in the high risk group.[36]

End organ ischemia was defined as follows:[35]

1. Cerebral ischemia was the presence of stroke or transient ischemic attack at presentation before surgery;
2. Extremity ischemia was the presence of pain in extremities and/or loss of pulses and/or difference in arterial pressures in 4 extremities;
3. Mesenteric ischemia was the presence of abdominal tenderness and bowel paralyses or evaluation of ischemia by CT scan (when it was mentioned in medical records)
4. Renal ischemia was the presence of malperfusion by CT scan (renal infarction on CT or insufficient flow in the artery), whenever it was mentioned in medical records, although CT scan of 44 patients were reviewed by the expert and the student investigator was participated in the process.

Generalized ischemia was defined as follows:[33]

1. Presence of shock before surgery, which was the presence of significant drop in systolic blood pressure lower than 80 mm Hg, and in some cases presence of oliguria.
2. Cardiac tamponade was present, when, because of aortic rupture the large amount of blood was acutely accumulated in the pericardial cavity.

3. Myocardial ischemia was the presence of ST segment elevation of more than 0.1mV on ECG.

2.5 Data extraction

We created a codebook (Appendix 3) in order to name, describe, code and classify the study variables collected from the medical records. The centers utilized two types of medical records for each patient: an outpatient medical record (charts) and an inpatient medical record. Outpatient records document patients' future and ongoing follow-up and the inpatient records record hospitalizations. Other documents, which we used for data collection, were the surgical, anesthesia and perfusion protocols. Information about demographic characteristics, risk factors and comorbidities were extracted from the outpatient records. Information about operative characteristics, postoperative complications and in-hospital mortality were extracted from the inpatient records and protocols. We entered the data directly into the electronic database created in advance in SPSS.23 software.

2.6 Sample size

For the sample size calculation, we used the method proposed by Wang et al based on odds ratio for the parallel design.[46] Assumption of unequal sample sizes was used based on the existing evidence of women to men ratio of 1:2 in manifestation of acute aortic dissection.

$$N_m = \left(\frac{1}{KP_f(1-P_f)} + \frac{1}{P_m(1-P_m)}\right)\left(\frac{Z_{1-\frac{\alpha}{2}} + Z\,\text{power}}{LN(OR)}\right)^2$$

where

K is the ratio of females to males ($K=N_f/N_m$), considering 1:2 ratio, K=0.5,

P_f and P_m are the event (mortality) rates among females and males respectively,

$Z_{1-\alpha/2}$ is the percentile of the standard normal distribution and equal to 1.96 for the alpha of 0.05,

Z_{power} is the percentile of the standard normal distribution and equal to 0.84 for the power of 0.8.

OR is the odds ratio of death computed as $OR=P_f(1-P_m)/P_m(1-P_f)$

Considering $\alpha = 0.05$, power = 0.8, $P_m = 0.22$ and the adjusted OR 1.4,[26] we estimated the overall sample size to be 1631 participants (1087 males and 544 females).

Considering that the number of cases in two hospitals during the period of interest was approximately 200 (personal communication), which is smaller than the required sample size, we decided to enroll all patients who had intervention. Additionally, we estimated sample sizes for different powers and effect sizes (Appendix 4).

2.7 Data analysis

Continuous variables were reported as the means and standard deviations (SD), categorical variables as frequencies and proportions. Difference in patient profiles, disease manifestation as well as in-hospital complication between sexes were compared using Student-t test (for continuous variables), Chi-square test or Fisher exact tests (for categorical variables) as applicable (Secondary Objectives 1 and 2).

Predictors of in-hospital mortality of AAAD were explored using unadjusted and adjusted logistic regression analysis (Secondary Objective 3). Variables with missing values more than 10 % were excluded from the analysis. Univariate logistic regression was performed and clinically important variables and those with $p < 0.25$ were further included in multivariable logistic regression analysis. Variables were tested for potential multicollinearity. We used step-wise backward elimination procedure for model selection and the final model was selected using log-likelihood ratio test and Akaike information criterion.

To estimate the independent impact of sex on in-hospital mortality we conducted multivariable logistic regression analysis. We selected variables for the model considering published literature, clinical experts' opinion and results from the analysis of predictors of the in-hospital mortality (primary objective). To explore the temporal changes in patient outcomes of AAAD during the study period we included the study interval as a covariate into the logistic regression model adjusted for the LH score (Secondary Objective 4).

To estimate the predictive power of the LH score on in-hospital mortality among Armenian population with AAAD, we first tested individual components of LH score in univariable analysis, then all score components combined in multivariable analysis and then compared with the combined LH score in univariable regression analyses (Secondary Objective 5). We assessed models' calibration (using Hosmer–Lemeshow goodness-of-fit test) and discrimination (using area under the receiver operating characteristic (ROC) curve).[35,36] All results with the p value less than 0.05 were considered statistically significant. We performed analysis using SPSS 23 and Stata/SE 12.0 softwares.

2.8 Ethical considerations

The study was approved by the institutional review board (IRB) of the American University of Armenia. This was a retrospective chart review and involved no patient contact and no more than minimal risk to the participants. Patient identifiers were not recorded in the database and only aggregate results were reported.

3. Results

In total, we identified 802 potentially eligible patients who were admitted to either hospital during the study period: 103 from the AMC adult surgical database, 524 from the NMMC adult outpatient database and 175 from the NMMC surgical database. After removing duplicates and eliminating patients who did not meet the inclusion criteria, we identified 211 patients who underwent surgery for AAAD from January 1, 2008 to April 1, 2018. Detailed information on study sample selection is provided in Figure 1.

3.1 Baseline characteristics

Preoperative baseline characteristics are presented in Table 1. From the total 211 patients, who underwent surgery for acute A type aortic dissection 23 were from the AMC and 188 were from the NMMC. Mean age of the participants was 56.7 ± 9.4 years, and the majority were males (76.3%, n = 161). Females were significantly older than males (59.2 ± 10.3 vs. 55.8 ± 9.1, p = 0.027). The majority of patients (71.1%) were admitted to the hospital with DeBakey I dissection. Smoking status was 11-fold higher among males compared to females (71.4% vs. 6.4%, p < 0.001). The prevalence of systemic hypertension was 92.4 % and was not different among sexes. More than 95% of the patients mentioned having a sharp, abrupt and severe acute chest, back or abdominal pain at onset. Only 18.6% of patients were admitted to the hospital within 6 hours from symptom onset. Syncope was present in 23.3% of the cases.

3.1.1 Assessment of the AAAD severity at presentation: The Leipzig-Halifax (LH) score estimation

More than half of the patients (n=111) fell into the Penn non Aa group, which means they had either some type of end organ or generalized ischemia or both conditions (Table 2), with males more likely to fall into Penn non Aa ischemia (56.5% vs. 40.0%, p-value = 0.052). Shock, cardiac tamponade and myocardial ischemia were present in 11.8%, 13.3% and 5.7% of the cases respectively. History of CAD was present in 19.4 % of the patients, being slightly higher among males than females (24.4% vs. 10.0% p = 0.065). Critical preoperative state was present in 8.5% of the cases being not different between sexes. Estimated mean LH score for study participants was 7.1 ± 6.3. The total number and proportions of males and females in each LH score category are provided in Table 2.

3.2 Operative and postoperative characteristics

Operative and postoperative characteristics are presented in Table 3. The most prevalent procedure in both centers was on the ascending aorta with or without hemiarch replacement (79.1%). Procedures involving the root replacement by Bentall/Davids (9.5%), total arch replacement (4.7%) were performed rarely. Concomitant coronary artery bypass grafting was performed in 20.4% and concomitant peripheral artery procedure was performed in 5.7% of the cases. Decisions regarding the type of main procedure as well as concomitant procedures were made during the surgery and were based on the case and surgeon preference.

Axillar cannulation was the most common cannulation site during the surgery, which was performed in 97.2% of the cases. Deep hypothermic circulatory arrest (DHCA) was being performed in 87.0% of the cases. Among those who had DHCA, the mean DHCA time was 42.6 ± 27.1 minutes. About fifth (20.7%) of patients had DHCA time longer than 59 minutes, with no significant difference between sexes. Mean operation time and cardiopulmonary bypass time (CPB time) were 458.1 ± 174.4 and 245.4 ± 111.5 minutes respectively, both being significantly longer among males than females ($p<0.05$). About 43.1% of patients experienced long CPB time (i.e., CPB ≥240 minutes).

3.3 In-hospital mortality and complications

Details on in-hospital mortality and complications are provided in Table 4. More than two thirds of patients (72.5%, n = 153) developed at least one major in-hospital complication. Of the total 211 patients, 37 (17.5%) died during the hospitalization period, including six who died during the surgery. In hospital complications did not differ between the sexes.

3.4 Predictors of in-hospital mortality

Univariate logistic regression analysis showed that, compared to lower LH score group, medium and high LH score groups had significantly higher odds of mortality, OR = 3.013 (95% CI: 1.320 - 6.877) and OR = 3.867 (95% CI: 1.005 - 14.877) respectively. CBP time of 240 minutes or more was another significant predictor of mortality (OR = 3.964, 95 % CI: 1.837 - 8.552). Other univariate predictors are listed in Table 5.

To produce the final predictive model, we ran multivariable logistic regression analysis that included age, DeBakey 1, concomitant CABG, concomitant peripheral arterial procedure, surgical categories, LH score categories, CPB-time more than 240 minutes and ACCT as a continuous variable. Aortic valve regurgitation (AoR) was assessed inconsistently by specialists. Therefore, after consultation with clinical experts, the decision was made not to include it in the multivariable model, regardless of its statistical significance (p-value = 0.046) in univariable analysis. Left ventricular ejection fraction was another variable that was excluded from the multivariable model, since it is clinically strongly correlated with shock or tamponade. The latter two parameters were included in LH score calculation; however, no collinearity had been detected between LVEF and LH score.

After stepwise removal of all non-significant variables, the final model included LH score categories, CPB time more than 240 minutes as independent predictors of in-hospital mortality after surgical repair of AAAD (Table 6). The odds of death among patients with CBP time ≥ 240 minutes were 3.985 (95% CI: 1.812 - 8.762) times higher compared to that of for patients with shorter CBP time. Patients with moderate (OR = 2.889, 95% CI: 1.235-6.757), and high LH scores (OR = 4.529, 95% CI: 1.102 - 18.613), also experience greater odds of death compared to patients with low LH score. The Hosmer-Lemeshow goodness of fit for the model was not significant (chi square = 2.174, df = 8, p = 0.975), and the AUC ROC = 0.733 (Figure 2). Table 6 represents the final predictive model. In the Appendix 5 the steps of the model development are provided.

3.5 The independent effect of sex on in-hospital mortality

To assess the independent effect of sex on in-hospital mortality we included clinically relevant potential confounders such as age, LH score and CPB time into the multivariable logistic regression model. Based on the adjusted model, sex was not an independent predictor of in-hospital mortality for patients with AAAD (OR = 0.526, 95 % CI: 0.22 - 1.43) (Table 7). The Hosmer-Lemeshow goodness of fit test demonstrated acceptable level of calibration for the model (chi square = 2.905, df = 8, p = 0.940).

3.6 Temporal changes in in-hospital mortality during the two study intervals

During the study period (2008-2018 years) surgical technique and equipment did not change that might have had a potential impact on patients' health outcomes. Therefore, we divided the study period into two equal intervals. The first interval included 2008-2012, the second interval included 2013-2018 (2018 year was not a complete year). In both centers, 75 and 136 patients underwent the surgery for AAAD during the first and second intervals respectively. In-hospital mortality tended to be higher in the first period (21.3% vs. 15.4%, p = 0.345) (Figure 3). After adjusting for LH score categories, the first period was not a significant predictor of mortality (OR = 1.540, 95% CI: 0.628 - 3.778, p = 0.345) (Table 9).

3.7 Predictive power of LH score for Armenian population

Figure 4 represents in-hospital mortality by LH groups. Univariate logistic regression analysis for the individual components of the LH score showed that only Penn class non Aa is a significant predictor of in-hospital mortality, OR = 3.411, 95% CI: 1.521 – 7.651. Multivariable analysis of the LH score components showed that Penn class non Aa is the independent predictor of mortality after adjusting for critical preoperative state and coronary artery disease, OR = 3.387, 95% CI: 1.495 – 7.671. Univariate logistic regression analysis showed that compared with lower LH score group, medium and high LH score groups had significantly higher odds of mortality, OR = 3.013, 95% CI: 1.320 - 6.877 and OR = 3.867, 95 % CI: 1.005 - 14.877 respectively (Table 9). The discrimination of the LH score for our study population when using the LH score as a single variable in the model was 0.634 (generated ROC AUC=0.634), indicating fair (poor) predictive power of the score for Armenian population. Figure 5 represents the ROC curve of the LH score by the univariable analysis (5a) and the components of the LH score by the multivariable analysis (5b) for study cohort.

4. Discussion

We conducted a study in Armenian surgical AAAD population to evaluate sex differences in in-hospital outcomes. In-hospital mortality of our patients was 17.5%, which was not significantly different between males and females. After adjusting for age, LH score and CPB time sex was not an independent predictor of mortality in our cohort.

The results of our study were consistent with several other studies' results.[27–29] The study by Pourafkari et al. conducted in Iran, that enrolled 192 patients from 2004 to 2015 and used propensity matching (hypertension, diabetes mellitus, smoking, age, prior stroke, history of bicuspid aortic valve and hemoglobin level) reported no difference in in-hospital mortality between sexes but reported higher mortality rates compared to our study (44.8% among males and 49.3% among females, $p = 0.603$ versus 17.4% among males and 18% among females, $p = 1.000$ respectively).[28] A study conducted by Conway et al. from Israel which includes 251 patients from 2000 to 2010 did not reveal a significant difference in operative mortality and in postsurgical complications such as deep sternal wound infection, prolonged ventilation, acute renal failure, hemodialysis, re-exploration because of bleeding and stroke between sexes.[29] The study by Fukui et al. conducted in Japan, which enrolled 504 patients from 2006 to 2013 showed no difference in 30-day postoperative mortality between sexes after adjusting for hypertension, myocardial ischemia, brain ischemia and shock/tamponade.[27] Reported overall mortality rate was about 3 fold higher in our study compared with Fukui et al. study (17.5% versus 5.2%). Some other studies showed difference in in-hospital mortality.[26,47] The study by Nienaber et al, drawn upon the multicenter IRAD data including patients from 1996 to

2001 period showed, that in-hospital mortality was significantly higher among women compared with men (31.9% vs. 21.9%, p=0.013) after adjusting for age, hypertension and the type of dissection; however, this difference was predominant in the 66-75-year-old group.[26] They explained this difference by the fact that women were presenting later to the hospitals compared with men, and the percentage of the shock and tamponade was much higher among women. In our study hours from symptom onset to presentation and also the presence of shock and cardiac tamponade were not different between sexes.

The mortality rates in our cohort were comparable with the study by Conway et al. mentioned above.[29] In this study the operative mortality rate was 17% for men and 19% for women. The mortality rates in our study were 17.4% and 18% for males and females respectively. Some postoperative complications in the study by Conway et al. were also comparable with our study results such as the rate of stroke, renal failure, postoperative hemodialysis and other complications such as reoperation for bleeding and mediastinitis. Another study covering 1995 to 2013 period and including 4,428 patients from IRAD data showed, that patients who underwent surgery for AAAD from 2007 to 2010 had the mortality rate of 15.8% and patients from 2010 to 2013 had the mortality rate of 18.4%,[20] which is consistent with our study results.

Our study showed that the LH score and CPB time greater or equal 240 minutes are independent predictors of in-hospital mortality. Two recent studies evaluated the role of LH score in predicting in hospital mortality among AAAD patients.[35,36] In the study by Leontyev et al. conducted in two centers in Germany and Canada enrolling 534 patients from 1996 to 2011 the LH scorecard was created.[35] In their study the critical preoperative state, visceral ischemia, coronary artery disease and age categories of 50-70 and greater than 70 were the independent predictors of in-hospital mortality. The in-hospital mortality was 18.7%, which is comparable with our study results. In the validation study of the LH score by Mejare-Berggren et al. conducted in Sweden and including 509 patients from 1996 to 2016 the in-hospital mortality was 11.5%, 23.4% and 43.2% in the low, medium and high LH score categories,[36] and were comparable with mortality rates observed in our study (9.4%, 23.8% and 28.6%). Megare-Berggrenn et al. showed that, the components of the LH score - critical preoperative state, Penn class non-Aa and coronary artery disease were independent predictors of in-hospital mortality after the surgery on AAAD.[36] Age was not a significant predictor of in-hospital mortality for Swedish population, which is comparable with our population and we calculated the LH score as it was calculated in the study by Megare-Berggrenn et al.. However, we included age in our final predictive model, because it is clinically important variable. The area under the ROC for our multivariable model on the components of the LH score was 0.67 which was comparable with the results of Mejare-Berggren's study (0.66).[36]

Mehta et al. study showed that age greater than "70 years, abrupt onset pain, abnormal ECG, any pulse deficit, kidney failure, hypotension/shock/tamponade" are the predictors of in-hospital death.[48] Olsson et al. showed that factors such as Penn class Ac, Penn class Abc, DHCA time greater than 59 minutes, concomitant CABG, supracoronary graft are the predictors of intraoperative and DeBakey type 1, Penn class Abc, Penn class non Aa, CPB time greater than 240 minutes, DHCA time greater than 59 minutes, age and concomitant CABG are the predictors of in hospital mortality.[43] Our study results are mostly consistent with the mentioned studies, because we adjusted for CPB time and LH score, which contains most of the factors used in the previous studies' multivariable models.

As during the study period there were no major changes in surgical procedures and no innovation of equipment that could potentially improve the outcomes, so we decided to divide the study period into two equal intervals to see whether there was the difference in in-hospital mortality, which could be explained by other factors (early diagnosis, increased clinical suspicion or better postoperative care). However, we did not find a significant difference between two periods being 21.3% and 15.4% respectively in the first and second periods. In the study by Pape et al. they showed significant increase in proportion of the patients, who underwent surgery for AAAD, being 78.7% in 1995 – 1999 and 90.2% in 2010 – 2013 period of time and mortality decreased over time, being 25% during 1995 – 1999 and 18.4% during 2010 – 2013, which they explained by the more rapid diagnosis, by the better performance of the surgical procedures and improved postoperative care.[20]

Strengths

Our study sample was representative for Armenia, because we included all centers performing AAAD surgery in Armenia. We used an established risk adjustment score in the analysis to address small sample size (ensured inclusivity of all the potential confounders (predictors) in one model). We assessed the validity of a risk adjustment score for Armenian population.

Limitations

It was a retrospective study with all the limitations that are specific for the nature of these studies. Data collection from the medical records could introduce the potential risk of non-correct interpretation of some variables. Twenty-three medical records were not available and for these cases we collected data from the discharge documents and electronic databases which generated missing information for some variables. Because of time constraints we were unable to assess the CT scans of 158 patients, which would have provided more precise evaluation of the preoperative ischemia and the size of the root and ascending aorta. Our study was underpowered to find a minimum detectable odds ratio of 1.4 in our primary outcome as desired (post-hoc calculated power was 15%). We did not take into consideration the postoperative factors (e.g., complications) in our predictive analysis. The study may have limited generalizability to population outside Armenia. Our results were limited to short-term, in-hospital outcomes although long-term outcomes are also important for these patients.

Conclusion

Our study did not find significant difference in in-hospital outcomes between sexes. Medium and high LH scores and longer CPB time were the predictors of in-hospital mortality of AAAD patients. There was no change in in-hospital mortality of AAAD over years. LH score has fair predictive value for Armenian population.

Recommendations

It will be valuable to evaluate the mid and long-term outcomes of this cohort; this information would be particularly important for patients with DeBakey type I dissection to follow the outcomes related to the descending aorta, which remains unprotected after the replacement of the ascending aorta. In addition, it would be valuable to initiate a collaboration with the IRAD, to internationally compare our surgical outcomes and other hospital performance measures.

References

1. Vilacosta I, San Román AJ. Acute aortic syndrome. *Heart*. 2001;85:365-368. doi:10.1136/heart.85.4.365.
2. Tsai TT, Nienaber CA, Eagle KA. Acute Aortic Syndromes. *Circulation*. 2005;112(24):3802-3813. doi:10.1161/CIRCULATIONAHA.105.534198.
3. Lemaire SA, Russell L. Epidemiology of thoracic aortic dissection. *Nat Rev Cardiol*. 2011;8(2):103-113. doi:10.1038/nrcardio.2010.187.
4. Chiu P, Miller DC. Evolution of surgical therapy for Stanford acute type A aortic dissection. *Ann Cardiothorac Surg*. 2016;5(4):275-295. doi:10.21037/acs.2016.05.05.
5. Coady MA, Rizzo JA, Goldstein LJ, Elefteriades JA. Natural history, pathogenesis, and etiology of thoracic aortic aneurysms and dissections. *Cardiol Clin*. 1999;17(4):615-635. doi:10.1016/S0733-8651(05)70105-3.
6. MCCLOY RM, Spittell Jr. JA, MCGOON DC. The Prognosis in Aortic Dissection (Dissecting Aortic Hematoma or Aneurysm). *Circulation*. 1965;31:665-669.
7. Li Y, Li L, Mu HS, Fan SL, He FG, Wang ZY. Aortic Dissection and Sudden Unexpected Deaths: A Retrospective Study of 31 Forensic Autopsy Cases. *J Forensic Sci*. 2015;60(5):1206-1211. doi:10.1111/1556-4029.12768.
8. Levinson DC, Edmeades DT, Griffith GC. Dissecting Aneurysm of the Aorta: Its Clinical, Electrocardiographic and Laboratory Features: A Report of Fifty-eight Autopsied Cases. *Circulation*. 1950;1(3):360-387. doi:10.1161/01.CIR.1.3.360.
9. Elveback L, Lie JT. Continued high incidence of coronary artery disease at autopsy in Olmsted County, Minnesota, 1950 to 1979. *Circulation*.

1984;70(3):345-349.
http://www.ncbi.nlm.nih.gov/pubmed/6744538%5Cnhttp://circ.ahajournals.org/content/70/3/345.full.pdf.

10. Roger VL, Weston SA, Killian JM, et al. Time trends in the prevalence of atherosclerosis: A population-based autopsy study. *Am J Med*. 2001;110(4):267-273. doi:10.1016/S0002-9343(00)00709-9.

11. Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. *Arch Intern Med*. 2000;160:5-10. doi:10.1001/archinte.160.19.2977.

12. Hagan PG, Nienaber C a, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283(7):897-903. doi:10685714.

13. Myrmel T, Larsen M, Bartnes K. The International Registry of Acute Aortic Dissections (IRAD) – experiences from the first 20 years. *Scand Cardiovasc J*. 2016;50(5-6):329-333. doi:10.1080/14017431.2016.1240829.

14. Howard DPJ, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM. Population-Based Study of Incidence and Outcome of Acute Aortic Dissection and Premorbid Risk Factor Control: 10-Year Results From the Oxford Vascular Study. *Circulation*. 2013;127(20):2031-2037. doi:10.1161/CIRCULATIONAHA.112.000483.

15. Debakey M, Henly W, Cooley D. Surgical management of dissecting aneurysms of the aorta. *J Thorac Cardiovasc Surg*. 1965;49.

16. Daily PO, Trueblood HW, Stinson EB, Wuerflein RD, Shumway NE. Management of Acute Aortic Dissections. *Ann Thorac Surg*. 1970;10(3):237-247.

doi:10.1016/S0003-4975(10)65594-4.

17. Spittell PC, Spittell JA, Joyce JW, et al. Clinical Features and Differential Diagnosis of Aortic Dissection: Experience With 236 Cases (1980 Through 1990). *Mayo Clin Proc*. 1993;68(7):642-651. doi:10.1016/S0025-6196(12)60599-0.

18. Sampson UKA, Norman PE, Fowkes FGR, et al. Global and regional burden of aortic dissection and aneurysms: Mortality trends in 21 world regions, 1990 to 2010. *Glob Heart*. 2014;9(1):171-180. doi:10.1016/j.gheart.2013.12.010.

19. Hirst Jr AE, Johns Jr VJ KJS. Dissecting aneurysm of the aorta : a review of 505 cases . *Med*. 1958;37(3):217-279.

20. Pape LA, Awais M, Woznicki EM, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the international registry of acute aortic dissection. *J Am Coll Cardiol*. 2015;66(4):350-358. doi:10.1016/j.jacc.2015.05.029.

21. Clouse WD, Hallett JW, Schaff H V., et al. Acute Aortic Dissection: Population-Based Incidence Compared With Degenerative Aortic Aneurysm Rupture. *Mayo Clin Proc*. 2004;79(2):176-180. doi:10.4065/79.2.176.

22. Mészáros I, Mórocz J, Szlávi J, et al. Epidemiology and Clinicopathology of Aortic Dissection. *Chest*. 2000;117(5):1271-1278. doi:10.1378/chest.117.5.1271.

23. Lindsay J, Hurst JW. Clinical features and prognosis in dissecting aneurysm of the aorta. A re-appraisal. *Circulation*. 1967;35(5):880-888. doi:10.1161/01.cir.35.5.880.

24. Landenhed M, Engstrom G, Gottsater A, Caulfield MP, Hedblad B. Risk Profiles for Aortic Dissection and Ruptured or Surgically Treated Aneurysms: A

Prospective Cohort Study. *J Am Heart Assoc*. 2015;4(1):1-10. doi:10.1161/JAHA.114.001513.

25. Suzuki T, Bossone E, Tolva V, et al. Aortic Dissection Insights From the International Registry of Acute Aortic. *Circulation*. 2006:1846-1860. doi:10.1161/CIRCULATIONAHA.105.000620.

26. Nienaber CA, Fattori R, Mehta RH, et al. Gender-related differences in acute aortic dissection. *Circulation*. 2004;109(24):3014-3021. doi:10.1161/01.CIR.0000130644.78677.2C.

27. Fukui T, Tabata M, Morita S, Takanashi S. Gender differences in patients undergoing surgery for acute type A aortic dissection. *J Thorac Cardiovasc Surg*. 2015;150(3):581-587.e1. doi:10.1016/j.jtcvs.2015.06.031.

28. Pourafkari L, Ghaffari S, Tajlil A, et al. Gender-related differences in presentation and outcome of acute type a aortic dissection. *Int Cardiovasc Res J*. 2017;11(3):89-95.

29. Conway B, Stamou S, Kouchoukos N, Lobdell K, Hagberg R. Effects of Gender on Outcomes and Survival Following Repair of Acute Type A Aortic Dissection. *Int J Angiol*. 2014;24(02):093-098. doi:10.1055/s-0034-1396341.

30. Trimarchi S, Nienaber C a, Rampoldi V, et al. Contemporary results of surgery in acute type A aortic dissection: The International Registry of Acute Aortic Dissection experience. *J Thorac Cardiovasc Surg*. 2005;129(1):112-122. doi:10.1016/j.jtcvs.2004.09.005.

31. Czerny M, Schoenhoff F, Etz C, et al. The Impact of Pre-Operative Malperfusion on Outcome in Acute Type A Aortic Dissection: Results From the GERAADA

Registry. *J Am Coll Cardiol*. 2015;65(24):2628-2635. doi:10.1016/j.jacc.2015.04.030.

32. Conzelmann LO, Weigang E, Mehlhorn U, et al. Mortality in patients with acute aortic dissection type A: Analysis of pre- and intraoperative risk factors from the German Registry for Acute Aortic Dissection Type A (GERAADA). *Eur J Cardio-thoracic Surg*. 2016;49(2):e44-e52. doi:10.1093/ejcts/ezv356.

33. Augoustides JG, Geirsson A, Szeto WY, et al. Observational study of mortality risk stratification by ischemic presentation in patients with acute type A aortic dissection: the Penn classification. *Nat Clin Pract Cardiovasc Med*. 2008;6(2):140-146. doi:10.1038/ncpcardio1417.

34. Kimura N, Ohnuma T, Itoh S, et al. Utility of the Penn classification in predicting outcomes of surgery for acute type a aortic dissection. *Am J Cardiol*. 2014;113(4):724-730. doi:10.1016/j.amjcard.2013.11.017.

35. Leontyev S, Légaré JF, Borger MA, et al. Creation of a Scorecard to Predict In-Hospital Death in Patients Undergoing Operations for Acute Type A Aortic Dissection. *Ann Thorac Surg*. 2016;101(5):1700-1706. doi:10.1016/j.athoracsur.2015.10.038.

36. Mejàre-Berggren H, Olsson C. Validation and Adjustment of the Leipzig-Halifax Acute Aortic Dissection Type A Scorecard. *Ann Thorac Surg*. 2017;104(5):1577-1582. doi:10.1016/j.athoracsur.2017.05.010.

37. Aortic Aneurysm Global Statistics - Mortality, Burden; 2013. Available from: http://global-diseases.healthgrove.com/l/130/Aortic-Aneurysm.

38. Andreasyan D, Bazarchyan A, Manukyan S, et al. *Health System Performance*

Assessment; National Institute of Health Named after Academician S. Abdalbekyan, MOH, RA, 2016.

39. Nork Marash Medical Center: Welcome to Nork-Marash Medical Center; 2012. Available from: http://www.nmmc.am/index.php?lang=en.

40. Chikwe J, Cavallaro P, Itagaki S, Seigerman M, Diluozzo G, Adams DH. National outcomes in acute aortic dissection: Influence of surgeon and institutional volume on operative mortality. *Ann Thorac Surg*. 2013;95(5):1563-1569. doi:10.1016/j.athoracsur.2013.02.039.

41. Սրտային վիրաբուժության բաժանմունք - ԱՍՏՂԻԿ ԲԿ. http://astghikmc.am/en/heart-surgery-2/. Accessed February 5, 2018.

42. Erbel R, Aboyans V, Boileau C, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;35(41):2873-2926. doi:10.1093/eurheartj/ehu281.

43. Olsson C, Hillebrant CG, Liska J, Lockowandt U, Eriksson P, Franco-Cereceda A. Mortality in acute type A aortic dissection: Validation of the Penn classification. *Ann Thorac Surg*. 2011;92(4):1376-1382. doi:10.1016/j.athoracsur.2011.05.011.

44. Khan MF, Fa X, Yu H Bin. Factors of Prolonged Intensive Care Unit Stay After Surgery in Patients with Type A Acute Aortic Dissection. *Biol Med*. 2016;9(1):1-5. doi:10.4172/0974-8369.1000367.

45. Pulido JN. Prediction of prolonged mechanical ventilation after cardiac surgery: An imperfect crystal ball. *J Thorac Cardiovasc Surg*. 2017;153(1):116-117. doi:10.1016/j.jtcvs.2016.09.009.

46. Wang H, Chow S, Li G, Hall H, Science C. On Sample Size Calculation Based on

Odds Ratio in Clinical Trials. *J Biopharm Stat*. 2002;12(4):471-483. doi:10.1081/BIP-120016231.

47. Maitusong B, Sun H-P, Xielifu D, et al. Sex-Related Differences Between Patients With Symptomatic Acute Aortic Dissection. *Medicine (Baltimore)*. 2016;95(11):e3100. doi:10.1097/MD.0000000000003100.

48. Mehta RH. Predicting Death in Patients With Acute Type A Aortic Dissection. *Circulation*. 2002;105(2):200-206. doi:10.1161/hc0202.102246.

Tables

Table 1. Patient baseline characteristics at presentation

Baseline characteristics	**Total (n=211)**	**Males (n=161)**	**Females (n=50)**	***P* value**
Age (years), mean (SD)	56.7(9.4)	55.8(9.1)	59.2(10.3)	0.027
Age ≥ 70 years, n (%)	16 (7.6)	9 (5.6)	7 (14.0)	0.065
DeBakey 1, n (%)	150 (71.1)	115 (71.4)	35 (70.0)	0.859
DeBakey 2, n (%)	61 (28.9)	46 (28.6)	15 (30.0)	
Smokers *, n (%)	108 (55.7)	105 (71.4)	3 (6.4)	0.000
Hypertension, n (%)	195 (92.4)	148 (91.9)	47 (94.0)	0.767
CAD, n (%)	41 (19.4)	36 (24.4)	5 (10.0)	0.065
DM, n (%)	7 (3.3)	5 (3.1)	2 (4.0)	0.671
Marfan syndrome, n (%)	3 (1.4)	2 (1.2)	1 (2.0)	0.558
COPD, n (%)	9 (4.3)	9 (5.6)	0 (0.0)	0.119
Previous aortic aneurysm, n (%)	5 (2.4)	4 (2.5)	1 (2.0)	1.000
Previous heart surgery, n (%)	4 (1.9)	3 (1.9)	1 (2.0)	1.000
Previous catheterization, n (%)	25 (11.8)	22 (13.7)	3 (6.0)	0.210
Presence of pain, n (%)	204 (96.7)	154 (95.7)	50 (100)	0.202
Pain location				
Chest, n (%)	115 (54.5)	88 (54.7)	27 (54.0)	0.242
Back, n (%)	7 (3.3)	4 (2.5)	3 (6.0)	
Abdominal, n (%)	5 (2.4)	4 (2.5)	1 (2.0)	
Chest and back, n (%)	34 (16.1)	22 (13.7)	12 (24.0)	
Chest and abdominal, n (%)	24 (11.4)	21 (13.0)	3 (6.0)	
Chest, back & abdominal, n (%)	19 (9.0)	15 (9.3)	4 (8.0)	
Other symptoms, n (%)	7 (3.3)	7 (4.3)	0 (0.0)	
Hours from symptom onset to presentation *				
Less or equal to 6 hours, n (%)	37 (18.6)	27 (17.6)	10 (21.7)	0.523
More than 6 hours, n (%)	162 (81.4)	126 (82.4)	36 (78.3)	
Hypotension, n (%)	57 (27.0)	42 (26.1)	15 (30.0)	0.588
Syncope, n (%)	47 (23.3)	35 (21.7)	12 (24.0)	0.703
Shock, n (%)	25 (11.8)	18 (11.2)	7 (14.0)	0.619
Pericardial effusion, n (%)	124 (58.8)	93 (57.8)	31 (62.0)	0.625
Cardiac tamponade, n (%)	28 (13.3)	21 (13.1)	7 (14.0)	0.815
Other than sinus rhythm, n (%)	10 (4.7)	6 (3.7)	4 (8.0)	0.252
Acute ischemia on ECG, n (%)	28 (13.3)	22 (13.8)	6 (12.0)	1.000
LVEF less than 35% *, n (%)	11 (5.2)	8 (5.0)	3 (6.0)	0.726
Bicuspid aortic valve, n (%)	12 (5.7)	9 (5.6)	3 (6.0)	1.000
AoR *, n (%)				
no AoR, n (%)	10 (4.8)	7 (4.4)	3 (6.0)	0.342
Mild AoR, n (%)	68 (32.4)	47 (29.4)	21 (42.0)	
Moderate AoR, n (%)	88 (41.9)	71 (44.4)	17 (34.0)	
Severe AoR, n (%)	44 (21.0)	35 (21.9)	9 (18.0)	
Cerebral ischemia, n (%)	10 (4.7)	7 (4.3)	3 (6.0)	0.704
Myocardial ischemia, n (%)	12 (5.7)	11 (6.8)	1 (2.0)	0.301
Renal ischemia, n (%)	6 (2.8)	5 (3.1)	1 (2.0)	1.000

Baseline characteristics	**Total (n=211)**	**Males (n=161)**	**Females (n=50)**	***P* value**
Visceral ischemia, n (%)	5 (2.4)	2 (1.2)	3 (6.0)	0.088
Extremity ischemia, n (%)	69 (32.7)	60 (37.3)	9 (18.0)	0.015
Critical preoperative state (combined variable), n (%)	18 (8.5)	13 (8.1)	5 (10.0)	0.772
Preoperative inotropic support, n (%)	10 (4.7)	8 (5.0)	2 (4.0)	1.000
Ventilation before surgery, n (%)	4 (1.9)	2 (1.2)	2 (4.0)	0.239
CPR before surgery, n (%)	8 (3.8)	5 (3.1)	3 (6.0)	0.397
Penn classification				
Penn class Aa, n (%)	100 (47.4)	70 (43.5)	30 (60.0)	0.052
Penn class Ab, n (%)	63 (29.9)	52 (32.3)	11 (22.0)	0.216
Penn class Ac, n (%)	32 (15.2)	26 (16.1)	6 (12.0)	0.652
Penn class Abc, n (%)	16 (7.6)	13 (8.1)	3 (6.0)	0.767
Penn class non Aa, n (%)	111 (52.6)	91 (56.5)	20 (40.0)	0.052

Note: All percentages were calculated after excluding missing values
* Smoking status was missing in 17 patients, hours from symptom onset to presentation was missing in 12 patients, AoR grade was missing in 1 patient, LVEF was missing in 1 patient

AoR = aortic valve regurgitation; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; DM = diabetes mellitus; ECG = electrocardiography; LVEF = left ventricular ejection fraction;

Table 2. Severity at presentation: Penn classification and the Leipzig-Halifax (LH) score *

	Total (n=211)	**Male (n=161)**	**Female (n=50)**	***P* value**
Critical preoperative state, n (%)	18 (8.5)	13 (8.1)	5 (10.0)	0.772
Preoperative inotropic support, n (%)	10 (4.7)	8 (5.0)	2 (4.0)	1.000
Mechanical ventilation, n (%)	4 (1.9)	2 (1.2)	2 (4.0)	0.239
Cardiopulmonary resuscitation, n (%)	8 (3.8)	5 (3.1)	3 (6.0)	0.397
Penn classification				
Penn class Aa, n (%)	100 (47.4)	70 (43.5)	30 (60.0)	0.052
Penn class Ab, n (%)	63 (29.9)	52 (32.3)	11 (22.0)	0.216
Penn class Ac, n (%)	32 (15.2)	26 (16.1)	6 (12.0)	0.652
Penn class Abc, n (%)	16 (7.6)	13 (8.1)	3 (6.0)	0.767
Penn class non Aa, n (%)	111 (52.6)	91 (56.5)	20 (40.0)	0.052
Coronary artery disease, n (%)	41 (19.4)	36 (24.4)	5 (10.0)	0.065
LH score *, mean (SD)	7.1 (6.3)	7.6 (6.3)	5.5 (6.2)	0.043
0 – 5, n (%)	96 (45.5)	68 (42.2)	28 (56.0)	
10 – 15, n (%)	101 (47.9)	82 (50.9)	19 (38.0)	0.227
20 – 25, n (%)	14 (6.6)	11 (6.8)	3 (6.0)	

*LH score is a composite score constructed by addition of scores assigned to each of the listed above risk factors (critical preoperative state = 10, Penn class-non Aa ischemia = 10, CAD = 5)

Table 3. Operative and postoperative characteristics by sex

	Total (n=211)	**Males (n=161)**	**Females (n=50)**	***P* value**
Surgical procedure				
Ascending/hemiarch, n (%)	167 (79.1)	125 (77.6)	42 (84.0)	
Bentall/Davids, n (%)	20 (9.5)	16 (9.9)	4 (8.0)	
Ascending/hemiarch & valve, n (%)	14 (6.6)	12 (7.5)	2 (4.0)	0.889
Total arch, n (%)	10 (4.7)	8 (5.0)	2 (4.0)	
Concomitant CABG, n (%)	43 (20.4)	35 (21.7)	8 (16.8)	0.428
Concomitant peripheral artery procedure, n (%)	12 (5.7)	12 (7.5)	0 (0.0)	0.073
Axillar cannulation, n (%)	205 (97.2)	155 (96.3)	50 (100)	0.753
DHCA type				
Partial DHCA, n (%)	171 (81.0)	131 (81.4)	40 (80.0)	
Full DHCA, n (%)	13 (6.2)	8 (5.0)	5 (10.0)	0.372
No DHCA, n (%)	27 (12.8)	22 (13.7)	5 (10.0)	
Operation time (min) *, mean (SD)	458.1 (174.4)	474.4 (181.5)	404.2 (137.6)	0.013
CPB time (min), mean (SD)	245.4 (111.5)	254.6 (116.9)	215.9 (86.6)	0.013
CPB time > 240 minutes, n (%)	91 (43.1)	77 (47.8)	14 (28.0)	0.015
ACCT (min), mean (SD)	141.3 (57.9)	146.0 (58.9)	126.1 (52.0)	0.033
DHCA time (min), mean (SD)[&]	42.6 (27.1)	44.1 (26.1)	38.2 (27.4)	0.208
DHCA time > 59 minutes, n (%)[&]	38 (20.7)	32 (23.0)	6 (13.3)	0.206
Minimal temp. (^{0}C)*, mean (SD)	22.9 (3.8)	22.8 (3.9)	23.2 (3.7)	0.526
Ventilation time > 48 hours*, n (%)	93 (48.4)	75 (51.7)	18 (38.3)	0.131
ICU stay > 120 hours *, n (%)	101 (50.0)	80 (51.9)	21 (43.8)	0.409
LOS (days), mean (SD)	26.3 (22.7)	26.0 (20.3)	27.1 (29.5)	0.779

Note: All percentages were calculated after excluding missing values.
[&]DHCA time was computed among patients who had DHCA (n=184)
* Operation time was missing in 3 patients, minimal temperature in 5 patients, ventilation time in 19 patients (6 patients died intraoperatively), ICU stay in 9 patients

ACCT = aortic cross clamp time; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest; ICU = intensive care unit; LOS = length of hospital stay.

Table 4. In-hospital mortality and complications by sex

	Total (n=211)	**Males (n=161)**	**Females (n=50)**	***P* value**
In-hospital mortality, n (%)	37 (17,5)	28 (17.4)	9 (18.0)	1.000
Any in-hospital complication*, n (%)	153 (72.5)	121 (75.2)	32 (64.0)	0.147
Patient with open chest after surgery, n (%)	32 (15.6)	26 (16.7)	6 (12.2)	0.652
Reoperation for bleeding, n (%)	34 (16.6)	28 (17.9)	6 (12.2)	0.509
Reoperation for other reason, n (%)	19 (9.3)	17 (10.9)	2 (4.1)	0.256
Rhythm disorder, n (%)	113 (55.1)	87 (55.8)	26 (53.1)	0.745
Pneumonia, n (%)	10 (4.9)	7 (4.5)	3 (6.1)	0.705
Acute respiratory distress syndrome, n (%)	27 (12.8)	23 (14.3)	4 (8.0)	0.334
Renal failure, n (%)	38 (18.5)	32 (20.5)	6 (12.2)	0.215
Renal failure requiring dialysis, n (%)	18 (8.8)	15 (9.6)	3 (6.1)	0.572
Acute heart failure, n (%)	24 (11.4)	18 (11.2)	6 (12.0)	0.805
Wound infection, n (%)	12 (5.9)	7 (4.5)	5 (10.2)	0.163
Mediastinitis, n (%)	4 (2.0)	4 (2.6)	0 (0.0)	0.574
Stroke, n (%)	11 (5.4)	9 (5.8)	2 (4.1)	1.000
Mesenteric ischemia, n (%)	4 (2.0)	4 (2.6)	0 (0.0)	0.574
Limb ischemia, n (%)	7 (3.4)	7 (4.5)	0 (0.0)	0.201

Note: All percentages were calculated after excluding missing values.
* Six patients died intraoperatively and were excluded from this analysis.

Table 5. Univariate logistic regression analysis of preoperative and intraoperative predictors of in-hospital mortality

Predictors	**OR**	**95% CI**	***P* value**
Male	0.959	0.419 - 2.196	0.921
Age (years)	1.093	0.295 - 4.045	0.894
DeBakey 1	1.929	0.797 - 4.664	0.145
Hypertension	1.531	0.333 - 7.044	0.584
CAD	1.708	0.750 – 3.890	0.202
HSO $\leq$ 6 hours	1.852	0.748 – 4.588	0.183
Hypotension	1.376	0.639 – 2.964	0.415
Syncope	1.150	0.500 – 2.645	0.742
Pericardial effusion	1.187	0.573 – 2.463	0.644
Tamponade	3.907	1.646 – 9.275	**0.002**
Shock	3.174	1.277 – 7.887	**0.013**
ECG changes showing any acute ischemia	0.781	0.254 – 2.407	0.667
LVEF $\leq$ 35%	4.516	1.298 – 15.718	**0.018**
AoR severe	0.286	0.084 – 0.981	0.046
Cerebral ischemia	5.281	1.445 – 19.299	**0.012**
Myocardial ischemia with ST segment elevation	0.931	0.331 – 2.617	0.893
Renal ischemia	0.939	0.106 – 8.281	0.955
Extremity ischemia	1.994	0.967 – 4.111	0.061
Critical preoperative state	1.385	0.429 – 4.475	0.586
Penn-non-Aa	3.411	1.521 – 7.651	**0.003**
LH low score category (reference)	1.000		
LH medium score category	3.013	1.320 – 6.877	**0.009**
LH high score category	3.867	1.005 – 14.877	**0.049**
Surgical procedure			
Ascending/hemiarch (reference)	1.000		
Bentall/Davids	1.296	0.402 – 4.179	0.664
Ascending/hemiarch & valve replacement	0.864	0.183 – 4.082	0.854
Total arch replacement	3.457	0.914 – 13.077	0.068
Concomitant CABG	1.877	0.841 – 4.189	0.125
Concomitant peripheral artery procedure	2.515	0.716 – 8.841	0.150
CPB time > 240 (minutes)	3.964	1.837 – 8.552	**0.000**
ACCT (minutes)	1.009	1.003 – 1.015	**0.002**
Minimal temperature (^{0}C)	0.929	0.841 – 1.025	0.143

ACCT = aortic cross clamp time; AoR = aortic valve regurgitation; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; DHCA = deep hypothermic circulatory arrest; ECG = electrocardiography; HSO = hours from symptom onset; LH = Leipzig-Halifax; LVEF = left ventricular ejection fraction.

Table 6. Multivariable logistic regression of predictors of in-hospital mortality

Predictors	**OR**	**95% CI**	***P* value**
Age	1.003	0.961 – 1.045	0.904
LH categories			
Low	1.000		
Medium	2.889	1.235 – 6.757	0.014
High	4.529	1.102 – 18.613	0.036
CPB time > 240 minutes	3.985	1.812 – 8.762	0.001

Table 7. Adjusted analysis for sex as a predictor of in-hospital mortality

Predictors	**OR**	**95% CI**	***P* value**
Male	0.562	0.222 – 1.425	0.225
LH categories			
Low	1.000		0.018
Medium	3.121	1.313 – 7.420	0.010
High	4.822	1.149 – 20.241	0.032
Age	0.999	0.958 – 1.042	0.977
CPB time > 240 minutes	4.429	1.957 – 10.027	0.000

Table 8. Adjusted analysis for period as a predictor of in-hospital mortality

Predictors	**OR**	**95% CI**	***P* value**
Period 2	1.000		
Period 1	1.540	0.628 – 3.778	0.345
CPB time > 240 minutes	4.963	1.994 – 12.354	0.001
LH categories			
Low	1.000		
Medium	2.946	1.257 – 6.904	0.013
High	4.131	0.980 – 17.417	0.053

Table 9. Adjusted analysis for period as a predictor of in-hospital mortality

Variables	**Univariable analysis**		**Multivariable analysis**	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Critical preoperative state	1.385 (0.429-4.475)	0.586	1.145 (0.340-3.860)	0.827
Penn class non Aa	3.411 (1.521 - 7.651)	0.003	3.387 (1.495-7.671)	0.003
Coronary artery disease	1.708 (0.750-3.890)	0.202	1.752 (0.746-4.116)	0.198
LH score category				
0-5 *(reference)*	1.000			
10-15	3.013 (1.320-6.876)	0.009	-	
20-25	3.867 (1.005-14.867)	0.049		

ROC AUC = 0.668 for the multivariable analysis; and ROC AUC = 0.634 for LH score in a univariable model

Figures

Figure 1. Flow chart of the study sample selection in NMMC and AMC

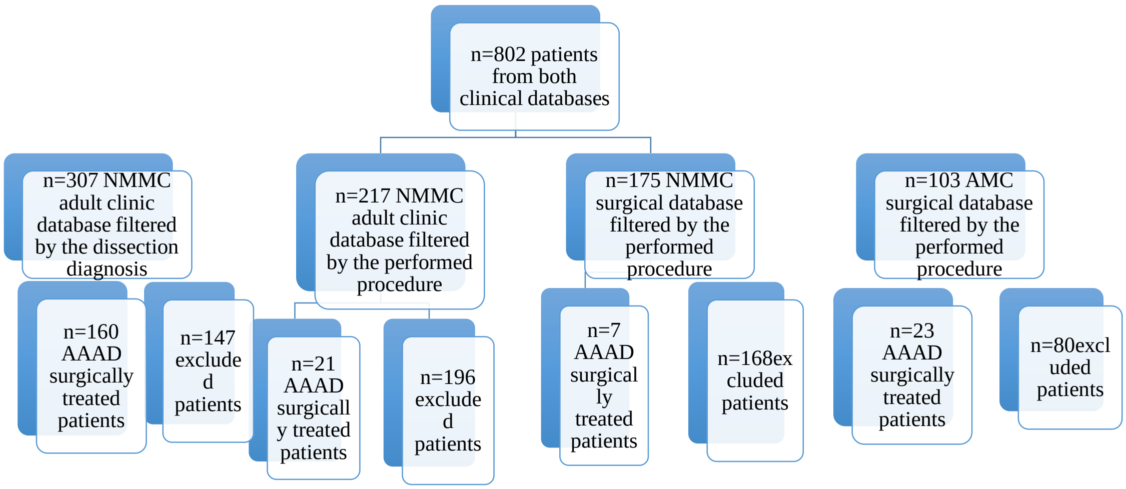


Figure 2. Receiver operating characteristic curve of the final predictive model of in-hospital mortality

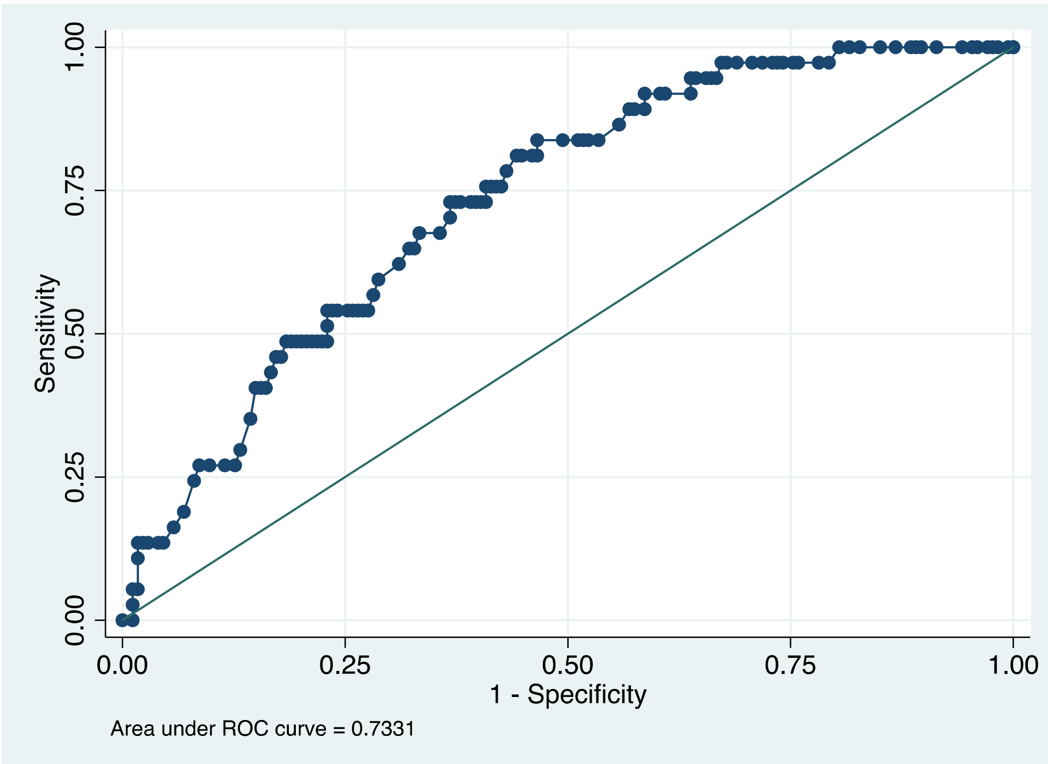
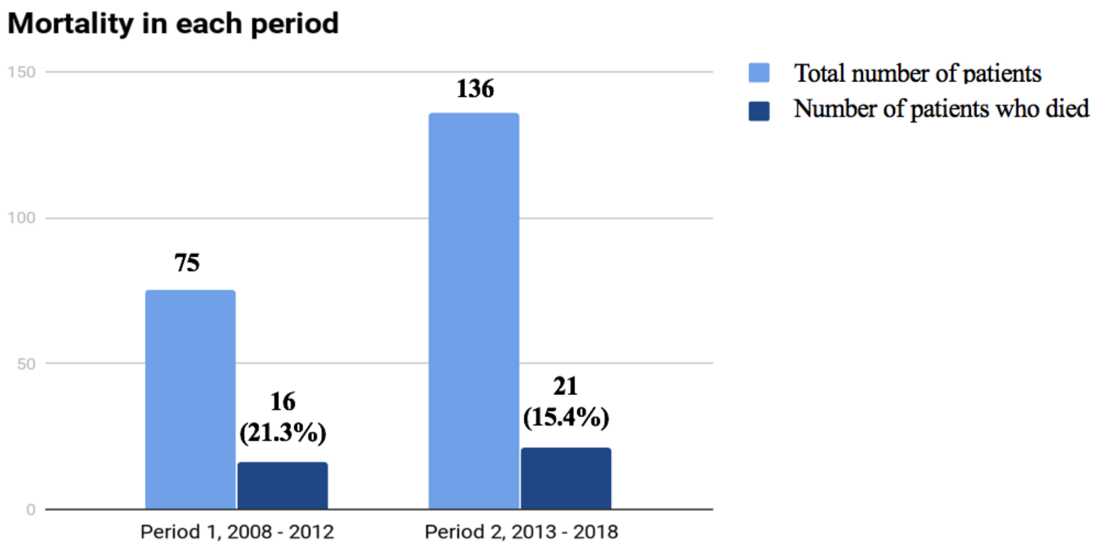
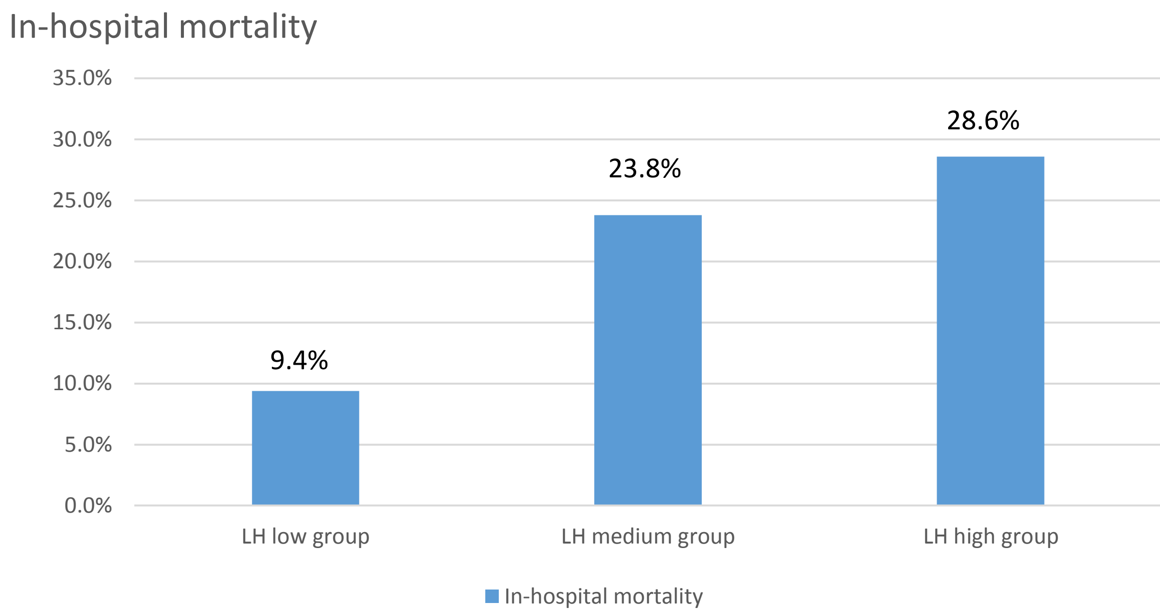


Figure 3. Temporal changes in in-hospital mortality during the two study intervals



	Period 1: 2008-2012	Period 2: 2013-2018
Total number of patients	75	136
In hospital mortality, n(%)	16 (21.3)	21 (15.4)

Figure 4. Mortality rate in each LH category



LH group	Low risk (LH score 0-5)	Medium risk (LH score 10-15)	High risk (LH score 20-25)
n	96	101	14
In-hospital mortality, n (%)	9 (9.4)	24 (23.8)	4 (28.6)

Figure 5. Receiver operating characteristic curve of LH-score of in-hospital mortality

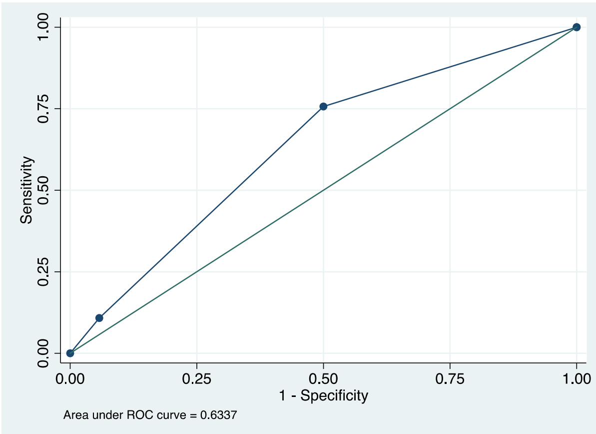


Figure 5a. ROC curve of the univariable model of the LH-score

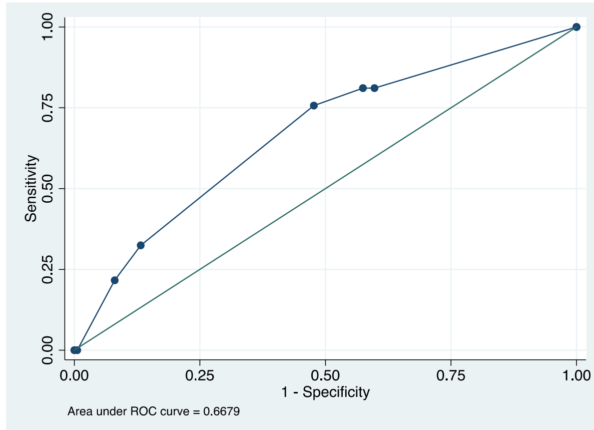


Figure 5b. ROC curve of multivariable model of components of LH score

Appendices

Appendix 1. Summary of the articles regarding to gender related differences in AAAD outcomes*

Author, year, country	Study population	Findings
Fukui, T et al, 2015, Japan.[27]	n=504 patients 245 women 259 men age≥70 218 (43.3%) patients, age<70 286 (56.7%) patients	Operative mortality: F: 4.5%, M: 5.8%, p=0.6463 35.5±24.9 months' mortality F: 15.5%, M: 9.3%, p-value not defined
Nienaber, Ch.A et al, 2004, (IRAD data).[26]	n=1078 732 men 346 women mean age=62.4±14.1 n=549 underwent surgery for AAAD 388 men 161women	Surgical mortality from AAAD: Men: 21.9%, women: 31.9% p=0.013 In-hospital complications 1. Cardiac tamponade: Men: 10.5%, Women: 16.5% p-value=0.007 2. Hypotension: Men: 23.9% Women: 34.1% P=0.001
Pourafkari, L. et al, 2017, Iran.[28]	n=192 71 females 121 males after propensity matching 67 females mean age 65.3±14 67 males mean age 59.3±12.6 p value=0.01	Hospital mortality: (variables such as hypertension, diabetes mellitus, smoking, age, prior stroke, history of bicuspid aortic valve and hemoglobin level were used to calculate propensity score) Male: 44.8%, Female: 49.3% P-value=0.603
Conway, B. et al, 2015, Israel.[29]	n=251 172 men 79 women median age=67 (range, 20-87 years)	Operative mortality Men: 17.0%, women: 19.0% p-value=0.695 Early Postoperative outcomes 1. Atrial fibrillation - Men: 25.0%, women: 26.0%, p-value 0.851 2. Stroke - Men: 8.0%, women: 5.0% p-value 0.415
Maitusong, B. et al, 2016, China.[47]	n=400 304 men 96 women mean age=50.7±12.7 n=40 underwent surgery for AAAD 30 men, 10 women	Surgical mortality from AAAD Men: 13.3%, women: 40.0% p-value=0.04 (Fisher's exact test)

**All studies utilized a retrospective cohort design.*

Appendix 2. The list of the dependent and independent variables

Variable name	Variable type	Measure
Dependent Variables		
In-hospital mortality	Dichotomous	Yes/No
Stroke	Dichotomous	Yes/No
Renal Failure	Dichotomous	Yes/No
Mesenteric ischemia	Dichotomous	Yes/No
Limb ischemia	Dichotomous	Yes/No
Preoperative independent Variables		
Age	Continuous	18 and above
Sex	Dichotomous	Male/female
Smoking status	Dichotomous	Yes/No
Marfan syndrome	Dichotomous	Yes/No
Type of dissection	Dichotomous	DeBakey I/DeBakey II
Hypertension	Dichotomous	Yes/No
Diabetes mellitus	Dichotomous	Yes/No
Chronic obstructive pulmonary disease or other (COPD)	Dichotomous	Yes/No
History ischemic heart disease (IHD)	Dichotomous	Yes/No
Previous aortic aneurysm	Dichotomous	Yes/No
Previous dissection	Dichotomous	Yes/No
Previous cardiac surgery	Dichotomous	Yes/No
Previous heart catheterisation	Dichotomous	Yes/No
Hours of symptom onset	Continuous	0-336
Hypotension	Dichotomous	Yes/No
Shock	Dichotomous	Yes/No
Tamponade	Dichotomous	Yes/No
Left ventricular ejection fraction (LVEF)	Continuous	%
Sinus rhythm (SR)	Dichotomous	Yes/No
Aortic regurgitation (AoR)	Ordinal	Grade I, II, III, IV
Intramural hematoma (IMH)	Dichotomous	Yes/No
Myocardial ischemia	Dichotomous	Yes/No
Electrocardiogram (ECG) showing acute ischemic changes	Dichotomous	Yes/No
Troponin level	Continuous	
Creatine kinase-MB (CK-MB) level	Continuous	
Preoperative neurological deficit	Dichotomous	Yes/No
Spinal ischemia	Dichotomous	Yes/No
Renal ischemia	Dichotomous	Yes/No
Visceral ischemia	Dichotomous	Yes/No
Extremity ischemia	Dichotomous	Yes/No
Preoperative inotropic support	Dichotomous	Yes/No
Preoperative mechanical ventilation	Dichotomous	Yes/No
Preoperative cardiopulmonary resuscitation	Dichotomous	Yes/No
Operative and postoperative independent variables		
Type of surgery	Nominal	Total arch replacement

		Hemi arch replacement Root replacement
Concomitant coronary artery bypass grafting	Dichotomous	Yes/No
Concomitant mitral valve procedure	Dichotomous	Yes/No
Aortic valve repair or replacement	Dichotomous	Yes/No
Cannulation site	Dichotomous	Femoral/axillar
Operation time	Continuous	Minutes
Aortic cross clamp time	Continuous	Minutes
Deep hypothermic circulatory arrest (DHCA)	Dichotomous	Yes/No
DHCA time	Continuous	Minutes
Transfusion time	Continuous	Minutes
Minimal temperature	Continuous	Celsius
Open chest	Dichotomous	Yes/No
Ventilation time	Continuous	Hours
Intensive care unit (ICU) stay (hours)	Continuous	Hours
Reoperation for bleeding	Dichotomous	Yes/No
Any reoperation	Dichotomous	Yes/No
Pneumonia	Dichotomous	Yes/No
Dialysis	Dichotomous	Yes/No
Mediastinitis	Dichotomous	Yes/No

Appendix 3. Codebook

Variable name	Variable #	Variable name in SPSS	Description	Codes	Variable type	Notes
ID	1.	ID	ID number of the participant (001,002….)		Continuous	
Age	2.	age	Age of the participant during the surgery		Continuous	
Date of hospital admission	3.	AD	YY MM DD		Continuous	
Date of surgery	4.	Surgery_date	YY MM DD		Continuous	
Date of death	5.	DD	YY MM DD		Continuous	
Date of hospital discharge	6.	DDis	YY MM DD		Continuous	
Sex	7.	sex	Sex of the study participant	1=male 0=female	Dichotomous	
Smoking status	8.	Smoking	Smoking status of the participant at the time of admission	1=yes 0=no missing	Dichotomous	
Marfan syndrome	9.	Marfan	Whether the patient had Marfan syndrome	1=yes 0=no	Dichotomous	
Type of dissection	10.	Type_dissec	The type of dissection according to DeBakey	1=DeBakey1 0=DeBakey2	Dichotomous	
Hypertension	11.	HT	history of systemic hypertension	1=yes 0=no	Dichotomous	
Diabetes mellitus	12.	DM	history of DM	1=yes 0=no	Dichotomous	
Chronic obstructive pulmonary disease or other (COPD)	13.	COPD	history of COPD	1=yes 0=no	Dichotomous	
History of coronary artery disease (CAD)	14.	CAD	history of CAD	1=yes 0=no	Dichotomous	
Previous aortic aneurysm	15.	AA	history of aortic aneurysm	1=yes 0=no	Dichotomous	

Previous dissection	16.	P_dissection	history of previous dissection	1=yes 0=no	Dichotomous	
Previous cardiac surgery	17.	P_surgery	history of any cardiac surgery including CABG, mitral, aortic valve surgeries	1=yes 0=no	Dichotomous	
Previous heart catheterisation	18.	P_catheter	history of heart catheterisation	1=yes 0=no	Dichotomous	
Other comorbidities	19.	Comorb	History of other comorbidities	1=yes 0=no	Dichotomous	
Specify comorbidities	20.	Spec_comorb	Type of comorbidity	specify	String	
Presence of pain	21.	Pain_presence	Whether patient admitted with pain	1=yes 0=no	Dichotomous	
Pain presentation	22.	Pain	Presentation of pain at admission	0=other symptoms 1=chest 2=back 3=abdominal 4=chest and back 5=chest and abdominal 6=chest, back and abdominal	Categorical	
Hours from symptom onset to presentation	23.	HSO	How many hours ago symptoms started before admission		Continuous	
Hypotension	24.	Hypotension	Whether patient admitted with hypotension	1=yes 0=no	Dichotomous	
Shock	25.	Shock	Whether patient admitted with cardiogenic shock	1=yes 0=no	Dichotomous	
Tamponade	26.	Tamponade	Whether patient admitted with cardiac tamponade	1=yes 0=no	Dichotomous	

Syncope	27.	Syncope	Whether patient had syncope before surgery	1=yes 0=no	Dichotomous	
Left ventricular ejection fraction (LVEF)	28.	LVEF	LVEF at admission		Continuous	
Sinus rhythm (SR)	29.	SR	Whether the patient admitted with SR	1=yes 0=no	Dichotomous	
Aortic regurgitation (AoR)	30.	AoR	Whether the patient admitted with AR	1=yes 0=no	Dichotomous	
AoR grade	31.	AoR_grade	Mild=0-I Moderate=1.5-II Severe=2.5-4 grade	1=mild 2=moderat e 3=severe	Ordinal	
Intramural hematoma (IMH)	32.	IMH	Whether the patient admitted with IMH	1=yes 0=no	Dichotomous	
Myocardial ischemia	33.	MI	Whether the patient admitted with myocardial ischemia-ischemic changes on ECG (ST segment elevation or depression)	1=yes 0=no	Dichotomous	
Electrocardiogram changes showing ST segment elevation of 0.1mV and more	34.	ECG	Whether the ECG of the patient showed acute ischemic changes, ST segment elevation of 0.1mV and more	1=yes 0=no	Dichotomous	
Troponin level	35.	Troponin	The level of the cardiac troponin		Continuous	
Creatine-kinase MB	36.	CK_MB	The level of CK_MB		Continuous	
Preoperative neurological deficit (cerebral ischemia)	37.	Preop_Neuro_Def	Any neurological deficit at admission	1=yes 0=no	Dichotomous	

Spinal ischemia	38.	Spinal_ischemia	Spinal ischemia during admission	1=yes 0=no	Dichotomous	
Renal ischemia	39.	Renal_ischemia	Renal ischemia during admission	1=yes 0=no	Dichotomous	
Visceral ischemia	40.	Visceral_ischemia	Visceral ischemia during admission	1=yes 0=no	Dichotomous	
Extremity ischemia	41.	Extremity_ischemia	Extremity ischemia during admission	1=yes 0=no	Dichotomous	
Preoperative inotropic support	42.	Inotropic_support	Whether the patient receive preoperative inotropic support	1=yes 0=no	Dichotomous	
Preoperative mechanical ventilation	43.	Preop_ventilation	Mechanical ventilation before surgery	1=yes 0=no	Dichotomous	
Preoperative cardiopulmonary resuscitation	44.	Preop_resusc	Cardiopulmonary resuscitation before surgery	1=yes 0=no	Dichotomous	
Type of surgery	45.	Surgery_type	Type of surgery	0=ascending/hemiarc 1=Bentall and David procedures 2=asc./hemi arch +valve replace 3=total arch replacement	Categorical	
Concomitant coronary artery bypass grafting (CABG)	46.	Concom_CABG	Simultaneous CABG during ascending aortic repair	1=yes 0=no	Dichotomous	
Concomitant mitral valve procedure	47.	Concom_Mirtal_repair	Simultaneous mitral valve procedure during ascending aortic repair	1=yes 0=no	Dichotomous	
Aortic valve repair/ replacement	48.	Aortic_repair_raplace	Aortic valve repair or replacement during ascending aortic repair	1=aortic valve repair 2=aortic valve	Dichotomous	

				replacement		
Aortic valve type	49.	Valve_type		2=bicuspid 3=tricuspid		
Cannulation site	50.	Cannulation	Cannulation cite during surgery	1=femoral 2=axillar 3=direct aortic	Categorical	
Operation time	51.	Operation_time	duration of the surgery (from opening of the chest to closing)		Continuous	minutes
Cardiopulmonary bypass time	52.	CPB_time	Duration of the cardiopulmonary bypass in minutes		Continuous	
Aortic cross clamp time	53.	ACCT	Aortic cross clamp time		Continuous	minutes
Deep hypothermic circulatory arrest (DHCA)	54.	DHCA	presence of deep hypothermic circulatory arrest	1=yes 0=no	Dichotomous	
DHCA time	55.	DHCA_time	duration of DHCA		Continuous	minutes
Minimal temperature	56.	Minimal_temp	Minimal temperature during surgery		Continuous	celcius
Open chest	57.	Open_chest	Whether the patient was taken out from the surgery room with open chest	1=yes 0=no	Dichotomous	
Ventilation time	58.	Vent_time	The time during which the patient stay on ventilator including preoperative, during and postoperative period		Continuous	hours
Intensive care unit (ICU) stay	59.	ICU_stay	ICU stay after surgery		Continuous	hours
Length of hospital stay	60.	Hospital_stay	How many days patient stay in hospital		Continuous	days

Reoperation for bleeding (Reopening of the chest)	61.	Reop_bleeding	Reoperation for bleeding	1=yes 0=no	Dichotomous	
Any reoperation	62.	Reop_other	Reoperation for any reason	1=yes 0=no	Dichotomous	
Rhythm disorder	63.	Rhythm_disorder	Presence of any rhythm disorder after surgery	1=yes 0=no	Dichotomous	
Rhythm specify	64.	Rhythm_specify			String	
Pneumonia	65.	Pneumonia	Whether the patient had pneumonia after surgery	1=yes 0=no	Dichotomous	
Dialysis	66.	Dialysis	Hemodialysis after surgery	1=yes 0=no	Dichotomous	
Wound infection	67.	Wound_infection	Whether the patient had wound infection after surgery	1=yes 0=no	Dichotomous	
Mediastinitis	68.	Mediastinitis	Whether the patient had mediastinitis after surgery	1=yes 0=no	Dichotomous	
In-hospital mortality	69.	Mortality	Whether the patient die after surgery during hospitalization period	1=yes 0=no	Dichotomous	
Stroke	70.	Stroke	Whether the patient had new neurological deficit after surgery	1=yes 0=no	Dichotomous	
Renal Failure	71.	Renal_failure	Renal failure after surgery	1=yes 0=no	Dichotomous	
Mesenteric ischemia	72.	Mesenteric_ischemia	New mesenteric ischemia after surgery	1=yes 0=no	Dichotomous	
Limb ischemia	73.	Limb_ischemia	Limb ischemia after surgery	1=yes 0=no	Dichotomous	
Other complication	74.	Other_complication	Other complication after surgery	1=yes 0=no	Dichotomous	
Specify complication	75.	Specify_other	If other complication, describe		String	

Center	76.	Center	Astghik medical center, Nork Marash medical center	1=NMMC 0=AMC		
Information source	77.	Info_source		1=medical records 0=discharge documents		
	78.					

Appendix 4. Sample sizes for different powers and effect sizes

	Effect size		
Power	$p_1 = 0.22$ $p_2 = 0.32$ OR =1.66	$p_1 = 0.45$ $p_2 = 0.49$ OR=1.17	p_1=0.13 p_2=0.40 OR=4.46
0.4	251	2039	35
0.6	422	3429	57
0.8	675	5494	91
0.9	904	7355	122

Note: cell values represents the overall sample size (ex, n=675, male =450, female =225)
p_1 is the male's mortality, p_2 is the female's mortality, assumption on a male: female ratio in a sample is 2:1respectively).

Appendix 5. Derivation of predictive model

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	.002	.024	.011	1	.917	1.002	.957	1.050
	surgery_new_categ			1.850	3	.604			
	surgery_new_categ(1)	-.716	.738	.943	1	.332	.489	.115	2.074
	surgery_new_categ(2)	-.842	.885	.905	1	.341	.431	.076	2.442
	surgery_new_categ(3)	.178	.758	.055	1	.814	1.195	.271	5.274
	Concom_peripheric	.866	.730	1.408	1	.235	2.377	.569	9.937
	DeBakey_1	.843	.498	2.861	1	.091	2.323	.875	6.169
	Concom_CABG	.162	.508	.101	1	.750	1.175	.434	3.184
	CPB_categ	1.147	.553	4.293	1	.038	3.148	1.064	9.313
	ACCT	.005	.004	1.546	1	.214	1.005	.997	1.014
	LH_scores_categ			5.869	2	.053			
	LH_scores_categ(1)	.897	.457	3.858	1	.050	2.453	1.002	6.003
	LH_scores_categ(2)	1.527	.739	4.275	1	.039	4.607	1.083	19.598
	Constant	-4.373	1.606	7.411	1	.006	.013		

a. Variable(s) entered on step 1: Age, surgery_new_categ, Concom_peripheric, DeBakey_1, Concom_CABG, CPB_categ, ACCT, LH_scores_categ.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	8.569	8	.380

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	CPB_categ	1.383	.402	11.825	1	.001	3.985	1.812	8.762
	LH_scores_categ			7.412	2	.025			
	LH_scores_categ(1)	1.061	.433	5.992	1	.014	2.889	1.235	6.757
	LH_scores_categ(2)	1.510	.721	4.387	1	.036	4.529	1.102	18.613
	Age	.003	.021	.015	1	.904	1.003	.961	1.045
	Constant	-3.152	1.308	5.807	1	.016	.043		

a. Variable(s) entered on step 1: CPB_categ, LH_scores_categ, Age.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	2.174	8	.975

Appendix 6. Final model with sex as a main independent variable

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	CPB_categ	1.488	.417	12.746	1	.000	4.429	1.957	10.027
	LH_scores_categ			8.021	2	.018			
	LH_scores_categ(1)	1.138	.442	6.638	1	.010	3.121	1.313	7.420
	LH_scores_categ(2)	1.573	.732	4.621	1	.032	4.822	1.149	20.241
	Sex	-.576	.475	1.473	1	.225	.562	.222	1.425
	Age	-.001	.021	.001	1	.977	.999	.958	1.042
	Constant	-2.643	1.356	3.796	1	.051	.071		

a. Variable(s) entered on step 1: CPB_categ, LH_scores_categ, Sex, Age.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	2.905	8	.940