CLINICAL PREDICTION MODEL OF POSTOPERATIVE HYPOTENSION

DERIVATION AND VALIDATION OF CLINICAL PREDICTION MODEL OF POSTOPERATIVE CLINICALLY IMPORTANT HYPOTENSION IN PATIENTS UNDERGOING NONCARDIAC SURGERY

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LAY ABSTRACT

In patients undergoing noncardiac surgery, numerous patients will develop postoperative clinically important hypotension. This may lead to complications including death, stroke, and myocardial infarction. I performed a large observational study to examine which risk factors would predict clinically important postoperative hypotension. Once we have identified these risk factors, we will use them to conduct randomized trials in patients at risk of clinically important hypotension to determine if we can prevent major postoperative complications.

ABSTRACT

Introduction

Postoperative medical complications are often preceded by a period with hypotension. Postoperative hypotension is poorly described in the literature. Data are needed to determine the incidence and risk factors for the development of postoperative clinically important hypotension after noncardiac surgery.

Methods

The incidence of postoperative clinically important hypotension was examined in a cohort of 40,004 patients enrolled in the VISION (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation) Study. Eligible patients were ≥45 years of age, underwent an in-patient noncardiac surgery procedure, and required a general or regional anesthetic. I undertook a multivariable logistic regression model to determine the predictors for postoperative clinically important hypotension. Model validation was performed using calibration and discrimination.

Results

Of the 40,004 patients included, 20,442 patients were selected for the derivation cohort, and 19,562 patients were selected for the validation cohort. The incidence of clinically important hypotension in the entire cohort was 12.4% (4,959 patients) [95% confidence interval 12.1-12.8]. Using 41 variables related to baseline characteristics, preoperative hemodynamics, laboratory characteristics, and type of surgery, I developed a model to predict the risk of clinically important postoperative hypotension (bias-corrected C-statistics: 0.73) The prediction model was slightly improved by adding intraoperative variables (bias-corrected C-statistics: 0.75). A simplified

prediction model using the following variables: high-risk surgery, preoperative systolic blood pressure <130 mm Hg, preoperative heart rate >100 beats per minute, and open surgery, also predicted clinically important hypotension, albeit with less accuracy (bias-corrected C-statistics 0.68).

Conclusion

Our clinical prediction model can accurately predict patients' risk of postoperative clinically important hypotension after noncardiac surgery. This model can help identify which patients should have enhanced monitoring after surgery and patients to include in clinical trials evaluating interventions to prevent postoperative clinically important hypotension.

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LIST OF ABBREVIATIONS

ACEi	angiotensin-converting enzyme inhibitor
ADL	activities of daily living
aHR	adjusted hazard ratio
AKI	acute kidney injury
aOR	adjusted odds ratio
ARB	angiotensin II receptor blockers
aRR	adjusted relative risk
ASA	American Society of Anesthesiologists
BIS	bispectral index
bpm	beats per minute
CAD	coronary artery disease
CCSC	Canadian Cardiovascular Society Class
CI	confidence interval
CIH	clinically important hypotension
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CT	computed tomographic
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
EVAR	endovascular abdominal aortic aneurysm repair
HR	heart rate
IABP	intra-aortic balloon pump
IQR	interquartile range
MAP	mean arterial pressure
MI	myocardial infarction
MINS	myocardial injury after noncardiac surgery
PAR	population attributable risk
RCRI	Revised Cardiac Risk Index
RCT	randomized controlled trial
ROC	receiver operating characteristics
SBP	systolic blood pressure
SD	standard deviation
TURP	transurethral resection of the prostate
VIF	variance inflation factor

STUDY/TRIAL ACRONYMS

POISE	Perioperative Ischemic Evaluation Study
VISION	Vascular events in noncardiac surgery patients: a cohort evaluation

DECLARATION OF ACADEMIC ACHIEVEMENT

I am the primary author of all chapters included in this thesis. I am also primarily responsible for the statistical analyses, interpretation, and reporting of data. Patient data were collected by qualified teams led by Dr. P. J. Devereaux.

CHAPTER 1: INTRODUCTION

1.1 Background

Worldwide, over 230 million noncardiac surgeries are performed annually.[1] Over the last 100 years, significant advancements in surgical techniques and patient management have led to a major improvement in intraoperative mortality and patient-reported outcomes including health-related quality of life,[2,3] Despite these advancements, postoperative complications are still common; globally, over 10 million patients will suffer a postoperative medical complication. In surgical patients aged ≥45 years, more than 10% will suffer a major cardiovascular event within 30 days—namely, vascular mortality, myocardial infarction (MI), or stroke.[4] Moreover, over 18% of surgical patients will sustain a myocardial injury after noncardiac surgery (MINS) within 30-days, an independent risk factor for perioperative mortality.[5] These complications are often preceded by a period of clinically important hypotension (CIH). CIH is defined as systolic blood pressure (SBP) ≤90 mm Hg, which results in clinical intervention, including initiation or administration of crystalloid or colloid, blood transfusion, vasopressors, inotropes, or intra-aortic balloon pump (IABP).[6] During a period of significant hypotension, there is a decrease in perfusion of the vital organs (i.e., brain, heart, and kidneys). This ischemia can put the surgical patient at risk of major medical complications postoperatively. Data suggests that CIH is the main driver of postoperative complications in surgical patients.[6-8] If we identify early on which patients are at risk of developing CIH, monitor these patients closely, and intervene in a timely manner when CIH occurs, we could potentially prevent a significant proportion of patients from sustaining a major cardiovascular complication.

1.2 Clinically important hypotension

There is a strong association between CIH and postoperative cardiovascular complications. In the Perioperative Ischemic Evaluation-1 (POISE-1) trial, an international randomized controlled trial (RCT) of 8351 patients from 190 centres in 23 countries, CIH was shown to have the highest population attributable risk (PAR) compared to all other risk factors for death (adjusted odds ratio [aOR], 4.97; 95% confidence interval [CI], 3.62-6.81; PAR, 37.3%) and stroke (aOR, 2.14; 95% CI, 1.15-3.96; PAR, 14.7%).[6] PAR is defined as the proportion of cases that would not occur if the factor (e.g., CIH) were causal and eliminated. These findings demonstrate a strong association between CIH and death, suggesting that CIH may be part of the causal pathway leading to postoperative death and stroke. A similar association is seen between CIH and perioperative MI. In POISE-2, a factorial RCT of 10,010 patients from 135 centres in 23 countries, CIH that preceded perioperative MI was found to be an independent predictor of perioperative MI (adjusted hazard ratio [aHR], 1.37; 95% CI, 1.16-1.62; PAR 14.8%).[9] The available evidence demonstrates that CIH is strongly associated with postoperative mortality and cardiovascular complications.

1.3 Intraoperative hypotension and its predictors

Many observational studies have demonstrated a significant association between intraoperative hypotension and postoperative complications (Table 1). In a prospective cohort study of 1,064 patients who underwent noncardiac surgery, a multivariable model demonstrated that for every minute that a surgical patient remained hypotensive intraoperatively (i.e., SBP <80 mm Hg), there was an increased risk of 1-year mortality (adjusted relative risk [aRR], 1.04; 95% CI, 1.01-1.07).[10] In a retrospective cohort study of 18,756 patients from 6 Veterans Affairs medical centres, intraoperative hypotension, defined using absolute hemodynamic thresholds was

associated with increased 30-day mortality, namely SBP <70 mm Hg (aOR, 2.90; 95% CI, 1.72-4.89), MAP < 49 mm Hg (aOR 2.43; 95% CI, 1.29-4.61), or diastolic blood pressure (DBP) < 50 mm Hg (aOR, 3.18; 95% CI, 1.83-5.54) for more than or equal to 5 minutes. [11] Moreover, patients with a decrease in MAP to more than 50% from baseline for more than or equal to 5 minutes had an increased risk of 30-day and 1-year mortality (aOR, 2.72; 95% CI, 1.49-4.97).[11]

The available evidence supports that intraoperative hypotension is associated with postoperative mortality. Further evidence also supports that intraoperative hypotension can also lead to major postoperative cardiovascular events (i.e., MINS, MI, and stroke). In a single-centre case-control study of patients who underwent noncardiac and non-neurological surgery (42 cases, 252 controls), a MAP decrease of more than 30% from baseline was associated with an increased occurrence of postoperative stroke (aOR, 1.01; 95% CI, 1.00-1.03).[12] In a secondary analysis of the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study, (n=16,079), a prospective international cohort study of noncardiac surgery patients, intraoperative SBP <100 mm Hg was associated with MINS (aOR, 1.21; 95% CI, 1.05-1.39) and 30-day mortality (aOR, 1.81; 95% CI, 1.39-2.37).[13]

These observational studies demonstrate that intraoperative hypotension is an important determinant of postoperative cardiovascular events and mortality. The risk of these complications also increases as the duration of intraoperative hypotension increases. In a retrospective study of 24,120 patients undergoing noncardiac surgery, a “triple low” (i.e., intraoperative hypotension with mean arterial pressure (MAP) <75 mm Hg, low bispectral index (BIS), and low minimum alveolar concentration) was associated with an increased risk of 30-day mortality (adjusted hazard ratio [aHR], 3.96; 95% CI, 2.57-6.10).[14] When examined closely, surgical patients, who

experienced “triple lows” for less than 15 minutes ended up with the same 30-day mortality risk as those who did not experience “triple low” events. However, among patients who had “triple lows” for more than 60 minutes, there was a 4-fold increase in mortality.[14]

In a retrospective study of 33,330 patients undergoing noncardiac surgery in Cleveland Clinic, if the duration of intraoperative hypotension was 1-5 minutes, there was an increased risk of acute kidney injury (AKI) (aOR, 1.18; 95% CI, 1.06-1.31), MI (aOR, 1.30; 95% CI, 1.06-1.58), cardiac complications — a composite outcome of intraoperative and postoperative MI, congestive heart failure (CHF), and cardiac arrest (aOR, 1.35; 95% CI, 1.15-1.58), but not 30-day mortality (aOR, 1.16; 95% CI, 0.91-1.46). However, if the duration of hypotension increased to more than 20 minutes, the risk increased substantially for AKI (aOR, 1.51; 95% CI, 1.24-1.84), MI (aOR, 1.82; 95% CI, 1.31-2.55), cardiac complications (aOR, 1.95; 95% CI, 1.46-2.60), and became statistically significant for 30-day mortality (aOR, 1.79; 95% CI, 1.21-2.65). In a single-centre RCT of 20,239 patients undergoing noncardiac surgery, patients were randomized to receive an intraoperative alert for “double-low” events, i.e., MAP <75 mm Hg and BIS <45, versus no alerts. Patients who experienced “double-lows” for a duration of 1-30 minutes versus 0 minute, had an increased risk of 90-day mortality that was not statistically significant (aHR, 1.28; 95% CI, 0.91-1.80). However, when the duration of “double-low” increased to 31-60 minutes versus 0 minute, the risk increased and became statistically significant (aHR, 1.74; 95% CI, 1.13-2.70).[15] Substantial observational evidence suggests that patients who experienced an episode of intraoperative hypotension are at risk of postoperative complications. More importantly, this association seems to be associated strongly with the duration of hypotension.

Many clinical prediction models have been developed to predict surgical patients at risk of intraoperative hypotension. In a prospective observational cohort study of 193 patients undergoing noncardiac surgery, a model was developed to predict a composite of intraoperative hypotension (SBP <90 mm Hg for >5 minutes), a 35% decrease in MAP, or intraoperative bradycardia (HR <60 beats/min). A multivariable regression model identified the following independent variables: preoperative bradycardia or hypotension (heart rate <60 beats per minute or blood pressure <110/60 mm Hg) (aOR, 2.68; 95% CI, 1.16-6.22), age >65 years old (aOR, 2.90; 95% CI, 1.48-5.67), preoperative use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), or beta-blockers (aOR, 1.81; 95% CI, 0.88-3.71), Revised Cardiac Risk Index (RCRI) ≥3 (aOR, 2.24; 95% CI, 0.68-7.39), and major surgery (aOR, 3.17; 95% CI, 1.61-6.26). The discrimination of this regression model has been evaluated as good (concordance statistics [c-statistics] 0.75).[16] In a retrospective cohort study of 113 patients undergoing emergent craniotomy for traumatic brain injury, computed tomographic (CT) lesions (aOR, 19.1; 95% CI, 2.08-175.99), subdural hematoma (aOR, 17.9; 95% CI, 2.97-108.10), maximum CT lesion thickness (aOR, 1.1;95% CI, 1.01-1.13) and duration of anesthesia (aOR, 1.1; 95% CI, 1.01-1.30) were identified as risk factors for intraoperative hypotension (SBP <90 mm Hg).[17] Many risk factors have been identified for intraoperative hypotension, the most common ones are related to patient characteristics, type of surgery, and preoperative hemodynamics.

1.4 Postoperative hypotension

In POISE-2, although the incidence of intraoperative hypotension was more common, an appreciable proportion of patients experienced postoperative hypotension. The incidence of postoperative hypotension was 6.6% on the day of surgery, 4.6% on postoperative day 1, 1.2% on

postoperative day 2, 0.6% on postoperative day 3.[7] The most striking difference between intraoperative and postoperative period was the duration of hypotension. The median duration of intraoperative hypotension was 15 minutes (interquartile range [IQR] 5-30 minutes), 30 minutes (IQR 15-60 minutes) in the post-anesthetic care unit (PACU), and 150 minutes (IQR 60-310 minutes) on postoperative day 1.[7] Similar to POISE-2, a sub-study of VISION (n=14,687) found that 19.5% of patients experienced at least one episode of postoperative CIH. During the postoperative period (i.e., PACU to hospital discharge), CIH occurred most frequently on postoperative day 1 (11.6%). Patients who experienced an episode of postoperative hypotension were more likely to be at risk of postoperative major cardiovascular events (i.e., death, MINS, or stroke) (aOR, 2.14; 95% CI, 1.89-2.43). On the other hand, patients who experienced an episode of intraoperative hypotension did not have a statistically significant increase in the risk of major cardiovascular events (aOR, 1.18; 95% CI, 0.99-1.39).[18]

The same duration of postoperative CIH is likely to have the same impact as intraoperative CIH on postoperative complications. However, the evidence suggests that postoperative CIH is substantially longer in duration than intraoperative hypotension. This discrepancy is likely due to the fact that on surgical wards, routine measurement of patient vital signs occurs typically every 6-8 hours, thereby limiting timely intervention. Such infrequent and episodic observations (and related interventions) are in stark contrast to the current standard or continuous intraoperative vital signs monitoring, which facilitates immediate clinician response.[19] Moreover, in contrast to intraoperative care, on surgical wards, there is no healthcare professional standing beside a patient ready to respond immediately to hypotension.

Evidence supports that postoperative hypotension poses a significant risk for postoperative adverse events. Despite the risks conferred by postoperative CIH, there is no validated clinical prediction model to identify patients most likely to develop CIH following surgery. I hypothesize that risk factors for postoperative hypotension can be identified in the preoperative setting. A valid clinical prediction model is needed to inform who is at risk for CIH following noncardiac surgery to facilitate identifying patients who may benefit from enhanced monitoring after surgery and identify patients for trials of prevention.

1.5 Thesis objectives

In my thesis, I used the definition of the postoperative CIH as postoperative SBP ≤90 mm Hg, that received an intervention (i.e., crystalloid or colloid, blood transfusion, vasopressors, inotropes, or an IABP). The postoperative period was defined as the period from arrival in PACU to hospital discharge. The objectives of my thesis included the following:

1. to describe the incidence of postoperative CIH in noncardiac surgery patients;
2. to derive and validate a clinical prediction model of postoperative CIH in surgical patients who underwent noncardiac surgery using preoperative patient characteristics;
3. to derive and validate a simplified scoring system using preoperative patient characteristics; and
4. to derive and validate a clinical prediction model of postoperative CIH in surgical patients who underwent noncardiac surgery using preoperative patient characteristics and intraoperative variables.

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CHAPTER 2: METHODS

2.1 Study design

Data were analyzed from the VISION study, a prospective international cohort study that included 40,004 patients from 28 centres in 14 countries (North and South America, Africa, Asia, Australia, and Europe) recruited from August 2007 to November 2013 (ClinicalTrials.gov NCT00512109).

2.2 Eligibility criteria

Surgical patients ≥45 years old and underwent noncardiac surgery that required a general or regional (i.e. nerve block, spinal, or epidural) anesthesia were included in the study. Surgical patients who underwent a noncardiac surgery and did not require overnight hospital admission or received infiltrative (i.e., local) or topical anesthesia were excluded. Patients who were previously enrolled in the VISION study or did not consent to participate were also excluded. Research ethics board or Institutional review board approval was obtained at each participating site.

2.3 Data collection and monitoring

After determining eligibility and consent, research personnel asked a series of questions to the participants concerning their past medical and social history. Research personnel also reviewed the patient's chart for additional history. During the patient's postoperative hospitalization, the research personnel reviewed the medical records and recorded data on hemodynamics and outcome events. The research personnel contacted the patients by phone at 30-days and 1-year post-surgery. If an event had occurred, the research personnel contacted their physician to obtain appropriate documentation. Central data consistency checks and on-site monitoring were used as

part of the data quality process (iDataFax, McMaster University, Hamilton, Ontario, Canada). For on-site monitoring, the study biostatistician randomly selected patients with or without perioperative complications and then an external auditor evaluated the patient's medical records and all supporting documents to ensure data accuracy.

2.4 Statistical analyses plan

2.4.1 Statistical analyses

I used STATA MP version 15 (College Station, Texas) and R version 3.6.2 (R Development Core Team) for all analyses with *-rms* package used in R.

2.4.2 Descriptive statistics

Baseline characteristics were described using descriptive statistics. Continuous variables were reported using mean and standard deviation (SD) or median and interquartile range (IQR). Independent student T-test was used to describe the difference between the derivation and validation cohorts. Categorical and binary variables were reported using frequency distribution. χ^2 test was used to compare the difference between the derivation and validation cohorts. All tests were two-sided and significance was defined as $p < 0.05$.

2.4.3 Data splitting

A single data set's prediction model can lead to error due to overfitting. Therefore, the model should be validated. A simple validation method is data-splitting. This is completed by dividing half of the dataset as a "training" sample—used for model development and the other half of the dataset as the "test" sample—used for model validation. To use this method for binary

outcomes, the "test" sample should contain a minimum of 100 subjects with the outcome of interest. Given that the incidence of postoperative CIH is 12.4%, I anticipated that the number of participants with the outcome of interest would be sufficient. A disadvantage of this method is the reduction in the sample size for both model development and model testing. However, given the large cohort of 40,004 in this study, data-splitting, in this case, is not a problem because the sample size in the split sample is much larger than required based on simulation studies. If the split on the dataset is performed randomly, the result may be fortuitous. If the process was repeated with a different splitting of the dataset, the accuracy may be different. To address this issue, I split the dataset at the centre level (i.e. one hospital or multiple hospitals sharing the same administration). I selected centres with similar geographic location (i.e. country or region) and the most common type of surgical procedure to be allocated to either derivation or the validation cohort (Table 2, Table 3). This method would optimize the matching of the derivation and validation cohort.

2.4.4 Outcome variable

The outcome variable was the presence of postoperative CIH, defined as postoperative SBP ≤90 mm Hg, where a clinician had to intervene to improve the patient's hemodynamics during the postoperative period — post-anesthetic recovery room (PACU) to hospital discharge.

2.4.5 Development of clinical prediction model of postoperative CIH

I undertook a multivariable logistic regression analysis to develop a prediction model in which the dependent variable was the presence of postoperative CIH (Table 4). The independent variables were selected for entry into the model based on biological plausibility and a literature review of known associated factors related to intraoperative hypotension. I modeled continuous

variables (age, preoperative SBP, preoperative DBP, preoperative heart rate, preoperative hemoglobin, preoperative eGFR) using restricted cubic spline with three knots to allow for non-linear relationship. I used a preoperative eGFR value of 5 mL/min/1.73m^2 calculated using the CKD-Epi equation for patients who were receiving dialysis preoperatively.

2.4.6 Independent variables included in the model

I included the following preoperative patient characteristics: age, sex, living in a nursing home, assistance with daily living, history or current atrial fibrillation, congestive heart failure, previous cardiac arrest, thromboembolic disease, cerebral vascular disease, peripheral vascular disease, hypertension, chronic obstructive lung disease, diabetes, dialysis, coronary artery disease, recent high-risk coronary artery disease, and aortic stenosis. The following preoperative vital signs and laboratory characteristics were included: SBP, DBP, heart rate, hemoglobin, and estimated glomerular filtration rate (eGFR) (Table 4). The following surgical variables were included: thoracic aorta reconstruction surgery, aorto-iliac reconstruction surgery, peripheral vascular reconstruction surgery, extracranial cerebrovascular surgery, endovascular aortic aneurysm repair, complex visceral resection general surgery, partial or total colectomy or stomach surgery, other intra-abdominal surgery, head and neck resection of non-thyroid tumour, pneumonectomy, lobectomy, other thoracic surgery, urogenital or gynecologic visceral resection, urogenital or gynecologic cytoreductive surgery, non-radical hysterectomy, radical hysterectomy, radical prostatectomy, transurethral prostatectomy, major hip or pelvic surgery, internal fixation of the femur, knee arthroplasty, above knee amputation, lower leg amputation, craniotomy, major spine surgery, the timing of surgery (elective: >72 hours, urgent: 24-72 hours, emergent: <24 hours), and open versus endoscopic surgery.

2.4.7 Sample size and event rate

Based on simulation models, a prediction model with 10-15 events per covariate maintains model stability and minimizes the risk of model overfitting. [1] In the derivation cohort, the event rate of postoperative CIH was 2443 patients and I evaluated a total of 41 covariates; thus, there were 60 events to 1 covariate. Due to a large number of independent variables and my assumption that many independent variables would be predictors of the outcome, I, a priori, planned and undertook analyses to simplify the model using a backward elimination approach with a p-value >0.10 as a criterion for removal. The type of surgery was considered to be one information item. Therefore, I elected to force all types of surgeries into the final model. Multicollinearity was tested using the variance inflation factor (VIF). If two covariates were highly correlated (i.e., a VIF >5), the least significant variable was dropped from the model.[2]

2.5 Calibration and discrimination

Two statistical approaches were used to determine the accuracy of the model performance: calibration and discrimination. Calibration compares our logistics regression model (i.e., predictions) to the observed data. This would generate a graph with a proportion of observed patients with postoperative hypotension against the expected (predicted) proportion of cases defined by the model. If the observed proportions and the predicted proportions agree over the entire range of the probabilities, then the slope of the line would be equal to 1. Discrimination is the ability of the logistic regression model to differentiate the participants who will have the outcomes versus those who will not. Concordance statistics (C-statistics) is used to describe the Receiver Operating Characteristics (ROC) curve.

2.5.1 Model validation

Once a model was developed, I repeated the backward elimination procedure with a bootstrapping technique of 1000 samples and tested against the original data. I reported the model calibration curve and discrimination using a bias-corrected C-statistics. The full model as a risk-estimating equation was reported. This can be integrated into software for use on a website or a hand-held device. I applied the developed model to the validation cohort and reported the model calibration curve and C-statistics.

2.5.2 Development of a clinical prediction model using categorical variables

In the main model, a restricted cubic spline was used for continuous variables. However, it is difficult for clinicians to apply such a complex model. I elected to create another model by converting all continuous variables into categorical variables. This would facilitate its interpretation by clinicians with an illustration of odds ratios. In the main model, a restricted cubic spline was used to place knots in areas where data is clustered together. The knots joined together to obtain the "best fit" for models where a continuous variable has a non-linear relationship with the outcome of interest.[3] I used the three knots obtained from restricted cubic spline modeling to construct the categorical variables. The ranges in between those knots were selected as boundaries for the categorical that were rounded to the nearest clinically significant number.

2.6 Simplified score system

Given a large number of independent variables used in the main prediction model, I created a simplified model by using a risk index scoring system to allow for easier prediction. I selected four independent variables that made the greatest contribution to the prediction of postoperative

CIH based on Wald χ^2 statistics for inclusion in the simplified risk index. I reported model calibration and discrimination to compare the simplified model performance against the performance of the full prediction model.

2.7 Preoperative and intraoperative model

I created a secondary model that includes the same variables as the original model, plus intraoperative variables. These included: intraoperative SBP <90 mm Hg, heart rate (HR) <55 beats per minute (bpm), HR >100 bpm, and duration of surgery. These variables were selected based on the biological plausibility of affecting the probability of postoperative CIH. The likelihood ratio test was performed to assess the goodness of fit of these two models. Its performance was compared to that of the main model based on calibration and discrimination.

2.8 Sensitivity analyses and missing data

Research has demonstrated that antihypertensives, such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) continued perioperatively may increase postoperative cardiovascular adverse outcomes.[4] I suspect this was mediated by a period of perioperative hypotension. To address this issue, I created a secondary model that included the main preoperative variables and antihypertensive medication used and held during the perioperative period. Since two main antihypertensive drugs are ACEi/ARB and beta-blockers,[5] I included these two variables with the following 4 categories: Never on the medication, chronically on medication and stopped 24 hours before surgery, chronically on medication and continued preoperatively, and new initiation of antihypertensive agent. The performance of this secondary model to the main model based on calibration and discrimination.

To deal with missing data, I created a dataset using single stochastic conditional imputation with logistic regression for binary variables and predicted mean matching for continuous variables. The following variables were used to perform imputation: thoracic aorta reconstruction surgery, aorto-iliac reconstruction surgery, peripheral vascular reconstruction surgery, extracranial cerebrovascular surgery, endovascular aortic aneurysm repair, complex visceral resection general surgery, partial or total colectomy or stomach surgery, other intra-abdominal surgery, head and neck resection of non-thyroid tumour, pneumonectomy, lobectomy, other thoracic surgery, urogenital or gynecologic visceral resection, urogenital or gynecologic cytoreductive surgery, non-radical hysterectomy, radical hysterectomy, radical prostatectomy, transurethral prostatectomy, major hip or pelvic surgery, internal fixation of femur, knee arthroplasty, above knee amputation, lower leg amputation, craniotomy, major spine surgery, timing of surgery, and open versus endoscopic surgery, age, sex, living in a nursing home, assistance with daily living, history or current atrial fibrillation, congestive heart failure, previous cardiac arrest, thromboembolic disease, cerebral vascular disease, peripheral vascular disease, hypertension, chronic obstructive lung disease, diabetes, dialysis, coronary artery disease, recent high-risk coronary artery disease, aortic stenosis, preoperative SBP, preoperative DBP, preoperative HR, hemoglobin, and eGFR. The main model was applied to this new dataset, and its performance was evaluated based on calibration and discrimination. A priori, I decided if there was no significant difference in model performance, then the main model using complete case analysis would be sufficient.

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CHAPTER 3: RESULTS

3.1 Baseline characteristics

Of the 40,037 patients enrolled in VISION, 40,004 patients were included in these analyses. 20,442 patients from 14 centres were included in the derivation cohort and 19,562 patients from 14 centres were included in the validation cohort (Figure 1). The mean age was 64.0 (standard deviation 11.3). Half of the patients were women. The most common comorbidities were hypertension (20,152 patients, 50.5%), active cancer (9832 patients, 24.6%), and diabetes (8332 patients, 20.9%). The most common surgeries were low-risk surgery (14,383 patients, 36.0%), major general surgery (7950, 19.9%), and major orthopedic surgery (6982 patients, 17.5%). The most common types of anesthesia were general (29,073 patients, 72.7%) and spinal (9811 patients, 24.5%) (Table 5).

3.2 Incidence of postoperative clinically important hypotension

The overall incidence of postoperative CIH was 12.4 % (4959 patients) [95% CI, 12.1-12.8] (Table 6). Postoperative hypotension occurred most frequently on postoperative day 1 (2239 patients, 5.7%, 95% CI, 5.5-5.9), in PACU (1632 patients, 4.4%, 95% CI, 4.2-4.6), and on the day of surgery after PACU (1379 patients, 3.7%, 95% CI, 3.5-3.9), respectively.

3.3 Main model

Using a backward elimination procedure, out of 49 candidate predictor variables evaluated, 41 variables were retained in the final model. The final model included the following variables: age, sex, activities of daily living (ADL), atrial fibrillation, coronary artery disease, aortic stenosis, chronic obstructive pulmonary disease (COPD), diabetes mellitus, smoking, timing of surgery,

open surgery, endovascular abdominal aortic aneurysm repair (EVAR), thoracic aortic reconstruction, aorto-iliac reconstruction, peripheral vascular reconstruction, cerebrovascular surgery, complex visceral resection, stomach surgery, intra-abdominal surgery, head and neck resection, radical hysterectomy, radical prostatectomy, transurethral resection of the prostate (TURP), major hip/pelvic surgery, internal fixation of the femur, knee arthroplasty, above knee amputation, lower leg amputation, craniotomy, major spine surgery, preoperative systolic blood pressure, preoperative diastolic blood pressure, preoperative heart rate, preoperative eGFR, and preoperative hemoglobin. The likelihood ratio test of the final model compared to the original model with all 49 predictors was not statistically significant (p=0.92).

A restricted cubic spline was used for continuous variables and split into three knots. Age had the following knots: 50, 65, and 81 years of age. Preoperative SBP's knots occurred at the following levels: 112, 140, and 175 mm Hg. Preoperative DBP's knots occurred at the following levels: 62, 80, and 97 mm Hg. Preoperative heart rate's knots occurred at the following: 60, 77, and 96 beats per minute. Preoperative eGFR's knots occurred at the following: 48, 83, and 104 mL per minute. Preoperative hemoglobin's knots occurred at the following levels: 104, 132, and 153 g L^{-1}.

The relationship between postoperative CIH and the continuous variables were examined graphically. The incidence of postoperative CIH with respect to age (Figure 2) appears to increase in risk significantly from 45 to 70. The slope of the risk seemed to be unchanged from 70 to 84 years in age and then increased once again over age 84. Preoperative SBP has the highest risk of postoperative CIH below 100; it decreases and gradually flattens around SBP 150 mm Hg (Figure 3). Diastolic blood pressure follows a linear relationship graphically; its risk decreases as the

higher the baseline preoperative diastolic blood pressure (Figure 4). The incidence of postoperative CIH in patients who had surgery >72 hours was 12%, while in patients who had surgery 24-72 hours, it was 10%. In patients who had surgery within 24 hours, the incidence of postoperative CIH was 15% (Figure 5).

3.4 Model performance

The final model showed good discrimination (c-statistics: 0.74) in the derivation cohort. After bootstrapping technique, the model was still considered to be good (c-statistics bias-corrected: 0.73). When applied to the validation cohort, the final model maintained its ability to discriminate (c-statistics: 0.73) (Table 9). An inspection of the calibration plot demonstrated that the final model had good calibration with a small overestimation of postoperative CIH when the incidence was above 40% after bootstrapping technique (Figure 8). The good calibration was maintained in the validation cohort (Figure 9).

3.5 Clinical prediction model using categorical variables

The main model has demonstrated good calibration and good discrimination. However, this model is difficult to apply clinically due to the use of restricted cubic spline. To facilitate the clinical application of this prediction model, another model using only categorical variables was created. Continuous variables were converted to categorical variables using the knots defined by restricted cubic spline and rounded to the nearest clinically important cut-offs. The surgical variables that had the highest risk for postoperative CIH included specific types of surgeries and open procedures (aOR, 2.02; 95% CI, 1.73-2.35) (Table 7). The most common surgeries that were considered high risk included: pneumonectomy (aOR, 5.10; 95% CI, 1.92-13.51), complex

visceral resection (aOR, 4.24; 95% CI, 3.42-5.25), and major hip/pelvic surgery (aOR, 3.71; 95% CI, 3.16-4.36). Related to patient characteristics, the most significant risk factors were history of aortic stenosis (aOR, 1.90; 95% CI, 1.39-2.58), recent high-risk coronary artery disease (CAD) (aOR, 1.51; 95% CI, 1.03-2.19), and history or current atrial fibrillation (aOR, 1.42; 95% CI, 1.19-1.68) (Figure 6). With regards to preoperative hemodynamic measurements, preoperative SBP <110 mm Hg (aOR, 2.47; 95% CI, 2.06-2.98), DBP <60 mm Hg (aOR, 1.51; 95% CI, 1.24-1.83) and preoperative heart rate >100 beats per min (aOR, 1.96; 95% CI, 1.55-2.48) were the most significant risk factors or postoperative CIH.

This model demonstrated good calibration in both the derivation cohort (Figure 10) and the validation cohort (Figure 11). The model maintained good discrimination (c-statistics in derivation cohort: 0.74, c-statistics bias-corrected: 0.73, c-statistics in validation cohort: 0.72) (Table 9).

3.6 Simplified prediction model

Given the large number of variables included in the final model, it is difficult to apply this prediction model clinically. To simplify the model, I selected the variables that provided the most amount of information using Wald χ^2 statistics (Figure 7). Since the type of surgery is considered to be one information item, I included a list of high-risk surgeries for postoperative hypotension: major hip/pelvic surgery, knee arthroplasty, complex visceral resection, stomach surgery, lobectomy, other thoracic surgery, visceral resection, radical prostatectomy, and aorto-iliac reconstruction. Open surgery, preoperative heart rate, and systolic blood pressure were other variables that provided the most amount of information and were included in the simplified model

with a risk scoring system (Table 10). The variables in the simplified model were: high-risk surgery (present in 32% of patients, with a score of 5), open surgery (present in 78% of patients in derivation cohort, with a score of 4), systolic blood pressure <130 mm Hg (present in 67% of patients in derivation cohort, with a score of 3), and heart rate >100 bpm (present in 8% of patients in derivation cohort, with a score of 2) (Table 11). This simplified model had fair discrimination (c-statistics in derivation cohort: 0.68, c-statistics bias-corrected: 0.68, c-statistics in validation cohort: 0.68) (Table 9) and good calibration (Figure 12, Figure 13). However, given that there are fewer variables, its discrimination is lower than the final model. Postoperative CIH occurred in 3.4% of patients with a score of 0, 5.0% of patients with a score of 2, 8.7% of patients with a score of 5, 17.5% of patients with a score of 9, and 36.6% of patients with a score of 14 (Table 12).

3.7 A model including preoperative & intraoperative variables

A model was created using the same preoperative variables as the final model plus intraoperative variables. These intraoperative variables included intraoperative hypotension (SBP <90 mm Hg) (occurred in 46% of patients), intraoperative tachycardia (HR >100 bpm) (occurred in 16% of patients), intraoperative bradycardia (HR <55 bpm) (occurred in 24% of patients), and surgical time (mean 213.95, standard deviation [SD] 164.81). The likelihood ratio test of this model compared to the main model is statistically significant ($p<0.001$). Intraoperative hypotension (aOR, 1.64; 95% CI, 1.48-1.82) increased the risk of postoperative CIH. The duration of surgical procedure (aOR, 1.00; 95% CI, 1.00-1.00) was statistically significant for a slight increase in the risk of postoperative CIH. Intraoperative bradycardia (aOR, 1.04; 95% CI, 0.92-1.17) was not associated with postoperative CIH. Intraoperative tachycardia was associated with a decrease in postoperative CIH (aOR, 0.83; 95% CI, 0.72-0.95). This model maintained good

calibration compared to the main model (Figure 14, Figure 15); however, this model also overestimated the risk when the incidence is above 40%. On the other hand, this model's ability to discriminate was slightly better compared to the main model using only preoperative variables (c-statistics in derivation cohort 0.75, c-statistics bias-corrected: 0.75, c-statistics in validation cohort 0.73) (Table 9).

3.8 Sensitivity analyses

3.8.1 Antihypertensive agents

A secondary model was created using the preoperative variables in the main model and the two most common antihypertensive agents: ACEi/ARB and beta-blockers. In the ACEi/ARB group, 67% of patients were never on these antihypertensive drugs, 8% of patients were chronically on these drugs and stopped 24 hours before surgery, 24% of patients were chronically on these drugs and continued perioperatively, 0.6% of patients were started on these drugs before surgery. In the beta-blocker group, 82% of patients were never on these antihypertensive drugs, 2% of patients were chronically on these drugs and stopped 24 hours before surgery, 15% of patients were chronically on these drugs and continued perioperatively, 0.4% of patients were started on these drugs before surgery. The likelihood ratio test of this model compared to the main model was not statistically significant (p=0.17). Perioperative continuation of ACEi/ARBs in patients who were chronically on ACEi/ARB (aOR, 1.14; 95% CI, 1.02-1.29) was associated with an increased risk for postoperative CIH, while the association between perioperative use of beta-blockers and postoperative CIH was not statistically significant. This model maintained good calibration (Figure 16, Figure 17) and good discrimination (c-statistics in derivation cohort 0.74,

c-statistics bias-corrected 0.73, c-statistics in validation cohort 0.73) (Table 9), with minimal change compared to the main model.

3.8.2 Missing data

In the derivation cohort, the following data were missing: thoracic aortic reconstruction (3 entries), open surgery (2 entries), history of smoking (7 entries), patient need assistance with ADL (2 entries), history of aortic stenosis (9 entries), history of coronary artery disease (7 entries), history of hypertension (3 entries), history of diabetes mellitus (2 entries), preoperative systolic blood pressure (32 entries), preoperative diastolic blood pressure (120 entries), preoperative heart rate (70 entries), preoperative eGFR (1418 entries), and preoperative hemoglobin (716 entries) (Table 13). The calibration of the main model on the imputed data was good (Figure 18, Figure 19), and discrimination of the imputed data was good (c-statistics of derivation cohort 0.74, c-statistics bias-corrected 0.73, c-statistics of validation cohort 0.73) (Table 9).

CHAPTER 4: DISCUSSION

4.1 Principal findings

Among an international cohort of 40,004 patients that underwent noncardiac surgery, postoperative clinically important hypotension occurred in 12.4% of participants. Given there are over 200 million surgeries worldwide annually,[1] this suggests 25 million surgical patients will develop postoperative clinically important hypotension. This study demonstrated that postoperative CIH can be accurately predicted using preoperative patient characteristics and surgical information. The main predictors were the type of surgery performed. The ones that had the highest risk of postoperative CIH were thoracic surgery, general surgery, and orthopaedic surgery. This would allow clinicians to determine which patients were at a higher risk of postoperative complications at an early stage where the patients are seen in the preoperative clinic. This would enhance planning for the disposition of the highest patients to more advanced monitoring settings, such as the intensive care unit or prolonged stay in the post-anesthetic recovery room or to receive remote automated monitoring technology.[2]

The main model was able to predict postoperative CIH with good discrimination. However, it is a complex model to apply clinically. To facilitate the model's use, I created a secondary prediction model using only categorical variables. However, this process may lead to a loss of information by converting continuous variables to categorical variables.[3] The main model and the model using categorical variables were compared using discrimination and calibration, it was determined that there was minimal loss of information. Therefore, for clinical use, the model with categorical variables can be applied to predict a patient's risk of postoperative CIH.

Although the main model can accurately predict surgical patients at risk, there are numerous variables involved and it is difficult to use clinically. To facilitate this task, a simplified model was created using the following four variables: high-risk surgery, open surgery, preoperative systolic blood pressure <130 mm Hg, and preoperative heart rate >100 bpm. However, the use of this simplified model has a decreased ability to discriminate compared to the main model. When the patient in the operating room, the prediction model that incorporates intraoperative variables can be beneficial. This model is slightly better at discriminating patients at risk of postoperative CIH compared to the main model.

4.2 Interpretation of model

Our study revealed that the predictors that had the strongest influence on surgical patients' risk of postoperative CIH were surgical variables. The surgeries with the highest risk were pneumonectomy, complex visceral resection, major hip/pelvic surgery, knee arthroplasty, and lobectomy. These types of surgeries are at a high risk of bleeding, with over 2% risk of major bleeding.[4] This would create significant fluid shifts that may result in postoperative hemodynamic changes. Another possible explanation for this relates to the specific surgery involved. In pneumonectomies, excess intraoperative crystalloid administration is one of the risk factors that would put these patients at risk of postoperative pulmonary edema, with an incidence of 2-5%.[5] Once a patient develops post-pneumonectomy pulmonary edema, the mortality rate exceeds 50%.[6] Therefore, to avoid this severe adverse event, most clinicians would minimize crystalloid administered perioperatively, which would place the patient at risk of postoperative hypotension. Similarly, in visceral resections or knee replacement, intraoperative fluid administration is also minimized. This is due to the introduction of "enhanced recovery after surgery (ERAS)" as part of

a fast-track pathway for surgical patients.[7] By using a strict fluid management strategy in orthopaedic surgery, the evidence suggests that there is a reduction in postoperative infection, transfusion, organ dysfunction.[8] This strategy can result in decreased fluid administration and result in more significant fluid shifts causing postoperative hypotension. For patients who are considered high-risk for postoperative CIH, it may beneficial to proceed with a more liberal approach for intraoperative fluid administration.

The other surgical variable that contributes to postoperative hypotension is an open technique as opposed to an endoscopic or laparoscopic technique. Laparoscopic techniques have revolutionized surgical practice. For example, in the case of laparoscopic versus open cholecystectomy, there was a decrease in mean blood loss (158 versus 219 ml, $p=0.01$), a decrease in hospital stay (6.4 versus 9 days, $p<0.001$).[9] Whereas in open procedures, in addition to an increase in blood loss, fluid loss intraoperative is compounded by the effect of third-spacing during the first 72 hours postoperatively and intraoperative insensible loss.[10] Thus, all of these reasons would contribute to postoperative hypotension in a patient undergoing an open procedure.

Several patient characteristics that were predictive of postoperative CIH. One major risk factor was advanced age. This is likely due to the fact that elderly patients have decreased response to their autonomic system. It is recognized clinically that they have a higher incidence of orthostatic hypotension.[11] After surgery, there is blood loss and significant fluid shifts. With a decreased autonomic system response, elderly patients may not be able to compensate to these changes, and therefore this puts them at a higher risk of postoperative hypotension. Cardiac history including aortic stenosis, coronary artery disease, and atrial fibrillation were risk factors for postoperative CIH. Patients with aortic stenosis often have associated left ventricular diastolic

dysfunction. They are preload dependent and at risk of intraoperative hypotension.[12] The same pathophysiology would predispose these patients to postoperative hypotension. Patients with coronary artery disease and atrial fibrillation tend to become more labile hemodynamically during the perioperative period.[13] It is unclear if this is secondary to the patient's underlying condition or the cardiac medications (e.g. ACEi) that the patients commonly take chronically.

Frail patients who need assistance with ADLs are prone to labile blood pressure, with episodes of profound and prolonged hypotension.[14] A surgical patient's preoperative blood pressure is indicative of their risk of postoperative CIH. The lower the systolic and diastolic blood pressure, the higher the risk for postoperative hypotension. Moreover, a patient's increased preoperative heart rate is a risk factor for postoperative hypotension. This is likely due to the fact that a reflex tachycardia is a normal physiologic compensation mechanism for hypotension, to maintain cardiac output.[15] However, if the patient started the surgery with a relatively increased heart rate, there is little room for further physiologic compensation before CIH sets in.

4.3 Comparison to other models

To the best of our knowledge, I have developed the first model to predict postoperative clinically important hypotension. A previous clinical prediction model that explained risk factors for intraoperative hypotension has identified similar risk factors as our prediction model. In a prospective cohort study of 193 patients undergoing noncardiac surgery, preoperative hypotension, advanced age, major surgery were risk factors for intraoperative hypotension.[16] In a large retrospective cohort study of 58,458 patients undergoing noncardiac surgery, the investigators examined the risk factors for intraoperative cardiovascular events, defined as: hypotension—

decrease of MAP >30%, hypertension—increase of MAP >30%, bradycardia—HR <50 bpm, or tachycardia—HR >100 bpm. This study identified that the American Society of Anesthesiologists (ASA) score and revised cardiac risk index (RCRI) were predictive for intraoperative cardiovascular events.[17] My study's outcome of interest is different from that presented by Rohrig and colleagues and I did not use RCRI as a variable in our prediction model. However, by examining each component of RCRI, which includes: high-risk surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, pre-operative treatment with insulin, and preoperative creatinine >177.8 μmol L^{-1}, we note that several of the components of RCRI were the same risk factors that we identified in our prediction model for postoperative CIH. Similarly, a patient with a high ASA score is likely to have numerous comorbidities. Our prediction model examined each comorbid disease individually and determined the ones that would predict the risk of postoperative CIH.

4.4 Strengths and Limitations

The strengths of this study included its large representative sample of surgical patients who underwent noncardiac surgery from 28 centres and 14 countries. The quality of the data collection was rigorous. There was minimal missing data with near-complete 30-day follow-up. The statistical methods were rigorous and pre-specified.

There are some limitations to this study. The outcome of interest, clinically important hypotension, was not adjudicated. The detection of hypotension postoperatively was based on routine practice. In the surgical ward, vital signs are only taken every 6-8 hours,[18] this could have led to an underestimation of these events. There may be a residual confounding effect on the

identification of postoperative CIH. For example, an important confounder is the amount of intraoperative fluid administration. However, this information was not collected and could not be analyzed in the model including intraoperative variables.

Another limitation of this study is the fact that some variables that were statistically significant do not have a clear biological explanation. These included the following: male sex, diabetes, and timing of surgery. In the model including intraoperative variables, intraoperative tachycardia also did not have a clear reason to decrease postoperative CIH. I checked for possible correlation between high risk surgeries for postoperative CIH and sex differences. Females had a higher incidence of hip/pelvic surgery ($p<0.01$) and knee arthroplasty ($p<0.01$) (Figure 20). Females also had a higher incidence of open surgery compared to males (females 82.7% versus male 73.6%; $p<0.01$) (Figure 21). Moreover, I checked for possible correlation between preoperative hemodynamics compared to sex. There was no statistical difference between preoperative systolic blood pressure between males and females ($p=0.28$) (Figure 22). However, males had a slightly higher preoperative diastolic blood pressure (males: mean 80.4 mm Hg; 95% CI, 80.1-80.6 mm Hg versus females: mean 78.1 m Hg; 95% CI, 77.8-78.3 mm Hg; $p<0.01$) (Figure 23) and males had a slightly lower preoperative heart rate (males: mean 76.6 bpm; 95% CI, 76.2-76.8 bpm versus females: mean 78.9 bpm; 95% CI, 76.2-76.8 bpm; $p<0.01$) (Figure 24). One possible explanation why male sex has lower incidence of postoperative CIH may be related to the fact that a higher proportion of females had high-risk surgeries (hip/pelvic surgery and knee arthroplasty). Furthermore, males had a higher preoperative diastolic blood pressure and lower preoperative heart rate, all of which contributed to a lower incidence of postoperative CIH. Another explanation for the sex difference may be biological. Previous studies have demonstrated that

females have a blunted cardiovagal baroreflex response compared to males.[19] In the context of orthostatic changes, this altered response may contribute to an increased incidence of postoperative CIH in females.[20]

Several factors were explored to explain why diabetic patients had a lower incidence of postoperative CIH. Non-diabetic patients had a higher incidence of hip/pelvic surgery ($p<0.01$) and lobectomy ($p=0.03$) both of which are considered high-risk surgeries (Figure 25). On the other hand, diabetic patients had a slightly higher incidence of open surgery ($p<0.01$) (Figure 26). Diabetic patients had a slightly higher preoperative systolic blood pressure (diabetic: mean 145.8 mm Hg; 95% CI, 145.0-146.6 mm Hg versus nondiabetic: mean 140.7 mm Hg; 95% CI, 140.3-141.1 mm Hg; $p<0.01$) (Figure 27). There was no statistical difference in preoperative diastolic blood pressure between diabetic and nondiabetic patients ($p=0.15$) (Figure 28). In terms of preoperative heart rate, diabetic patients had a slightly higher heart rate (diabetic: mean 79.5 bpm; 95% CI, 79.0-80.0 bpm versus nondiabetic: mean 77.2 bpm; 95% CI, 77.0-77.5; $p<0.01$) (Figure 29). Overall, non-diabetic patients had a greater proportion of high-risk surgeries including hip/pelvic and lobectomy. Furthermore, diabetic patients had a slightly higher preoperative systolic blood pressure. These factors may contribute to the reasons why diabetic patients had a lower risk for postoperative CIH.

I examined for possible correlation with regards to the timing of surgery. A large proportion of high-risk surgeries were in the >72 hours group, including knee arthroplasty ($p<0.01$), complex visceral resection ($p<0.01$), lobectomy ($p<0.01$) and other thoracic surgery ($p<0.01$) compared to 24-72 hours and <24 hours (Figure 30). The 24-72 hour group had a higher proportion of open surgery compared to >72 hours and <24 hours ($p<0.01$) (Figure 31). There was no statistical

difference between >72 hours versus 24-72 hours with regards to preoperative systolic blood pressure (p=0.12) (Figure 32) or preoperative diastolic blood pressure (p=0.48) (Figure 33). 24-72 hours group had a higher preoperative heart rate compared to >72 hours (24-72 hours: mean 82.6 bpm; 95% CI, 81.8-83.3 bpm versus >72 hours: mean 77.9 bpm; 95% CI, 76.7-77.2 bpm; p<0.01) (Figure 34). It appears that a possible explanation for higher risk in the >72 hours group is correlated with a greater proportion of patients who had high-risk surgery.

Intraoperative tachycardia decreased the risk of postoperative CIH. One possible explanation for this may be related to the fact that in the operating room when intraoperative tachycardia occurs, anesthesiologists will increase crystalloid or colloid administration. Therefore, the risk of postoperative CIH may have decreased due to fluid administration as opposed to an association with intraoperative tachycardia. When I examine for possible correlation with other variables, patients who did not experience intraoperative tachycardia had a higher proportion of hip/pelvic surgery (p<0.01) or knee arthroplasty (p<0.01) (Figure 35). The patients who did not experience intraoperative tachycardia had a slight increase in open surgery (p=0.03) (Figure 36). The patients who experienced intraoperative tachycardia had a slightly higher preoperative systolic blood pressure (intraoperative tachycardia: mean 145.1 mm Hg; 95% CI, 144.3-146.0 mm Hg versus no intraoperative tachycardia: mean 140.9 mm Hg; 95% CI, 140.5-141.3 mm Hg; p<0.01) (Figure 37), a slightly higher preoperative diastolic blood pressure (intraoperative tachycardia: mean 83.3 mm Hg; 95% CI, 82.9-93.8 mm Hg versus no intraoperative tachycardia: mean 78.3 mm Hg; 95% CI, 78.1-78.5 mm Hg; p<0.01) (Figure 38), and a higher preoperative heart rate (intraoperative tachycardia: mean 90.0 bpm; 95% CI, 88.4-89.6 bpm versus no intraoperative tachycardia: mean 75.1 bpm; 95% CI, 74.9-75.3 bpm; p<0.01) (Figure 39). Therefore, another

possibility may be related to patients who didn't have intraoperative tachycardia had a greater proportion of high-risk surgeries, while patients with intraoperative tachycardia also had a higher preoperative systolic and diastolic blood pressure.

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CHAPTER 5: CONCLUSION AND FUTURE DIRECTIONS

5.1 Conclusion

I demonstrated that postoperative clinically important hypotension can be predicted in the preoperative setting. This prediction model will help physicians identify the patients who are at the highest risk for postoperative hemodynamic compromise. The current approach of routine monitoring in the surgical ward may be inadequate for these patients, as their prolonged episode of postoperative hypotension may lead to cardiovascular complications. This prediction model can be used as eligibility criteria for future trials related to remote automated, continuous monitoring devices. I believe that with early detection of abnormal vital signs, and appropriate intervention, we may be able to reduce postoperative complications in surgical patients.

CHAPTER 6: APPENDIX

6.1 Tables and Figures

Table 1: Observational and experimental studies on the association of intraoperative hypotension and postoperative outcomes

Author	Design	Population	Sample size	Intervention/Exposure	Results
Abbott 2018[1]	Prospective	Noncardiac	16,079	SBP < 100 mm Hg	MINS: aOR, 1.21 (1.05-1.39) Mortality: aOR 1.81 (1.39-2.37)
Babazade 2016[2]	Retrospective	Colorectal	2528	SBP < 80 mm Hg MAP < 55 mm Hg	No association between hypotension and surgical site infection SBP < 80: aOR 0.96 (0.84-1.11) MAP < 55: aOR 0.97 (0.81-1.17)
Bijker 2012[3]	Case-Control	Noncardiac and nonneurological	294 (42 cases, 252 controls)	MAP decrease > 30% of baseline	Increased occurrence of postoperative stroke aOR 1.013 99% CI (1.000-1.025)
Hsieh 2016[4]	Case-Control	Nonneurological, Noncarotid, Noncardiac	502 (104 cases, 398 controls)	MAP < 70 mm Hg	No difference in stroke 1.07 (0.76-1.53)
Levin 2015[5]	Retrospective	Noncardiac	35,314	MAP < 50 mm Hg	Increased mortality aOR 1.18 (1.06-1.32)
McCormick 2016[6]	Prospective observational	Noncardiac	20,239	Intraoperative alerts for MAP < 75 mm Hg and BIS < 45 versus no alerts	Automated alerts to double-low did not significantly lower 90-day mortality.
Monk 2015[7]	Retrospective	Mixed noncardiac	12,675	SBP < 67 mm Hg, MAP < 49 mm Hg, DBP < 33 mm Hg	Associated with increase in 30-day mortality MAP 40-49 aOR 2.43 (1.29-4.61) MAP <40 aOR 20.83 (8.88-48.82) SBP <70 aOR 2.90 (1.72-4.89)

aOR: adjusted odds ratio; CI: confidence interval; MAP: mean arterial pressure; MINS: myocardial injury after noncardiac surgery; SBP: systolic blood pressure

References

1. Abbott TEF, Pearse RM, Archbold RA, et al. A Prospective International Multicentre Cohort Study of Intraoperative Heart Rate and Systolic Blood Pressure and Myocardial Injury After Noncardiac Surgery: Results of the VISION Study. Anesthesia and analgesia 2018;126:1936-45.
2. Babazade R, Yilmaz HO, Zimmerman NM, et al. Association Between Intraoperative Low Blood Pressure and Development of Surgical Site Infection After Colorectal Surgery: A Retrospective Cohort Study. Ann Surg 2016;264:1058-64.
3. Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. Anesthesiology 2012;116:658-64.
4. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM. The Association Between Mild Intraoperative Hypotension and Stroke in General Surgery Patients. Anesthesia and analgesia 2016;123:933-9.
5. Levin MA, Fischer GW, Lin HM, McCormick PJ, Krol M, Reich DL. Intraoperative arterial blood pressure lability is associated with improved 30 day survival. Br J Anaesth 2015;115:716-26.
6. McCormick PJ, Levin MA, Lin HM, Sessler DI, Reich DL. Effectiveness of an Electronic Alert for Hypotension and Low Bispectral Index on 90-day Postoperative Mortality: A Prospective, Randomized Trial. Anesthesiology 2016;125:1113-20.
7. Monk TG, Bronsert MR, Henderson WG, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology 2015;123:307-19.

Table 2: Centres in derivation or validation cohort

Derivation cohort	Validation cohort
Winnipeg (1697)	Cleveland (1248)
Paris (598)	Poland (982)
Bogota (628)	Porto Algere (1001)
HGH (751)	Liverpool, UK (722)
Henderson/Juravinski (3884)	UCH London, UK (880)
Victoria Hospital, London, ON (747)	St.Joe's (1003)
MUMC (642)	Edmonton (1580)
India Christian (1549)	India St-John (1996)
Burcaramanga (1392)	Lima (1539)
Sao Paulo (1503)	South Africa (1489)
Madrid (1764)	Barcelona (1985)
Hong Kong (4413)	Kuala Lumpur (2047)
Leeds, UK (733)	London, UK (2007)
St. Louis (141)	Sydney (1083)

Table 3: Recruitment by country and centre

Continent, country, city, centre	Participants (n=40,004)
North America	(11,693)
Canada	
Hamilton	
Juravinski Hospital and Cancer Centre	3884
Saint Joseph's Healthcare	1003
Hamilton General Hospital	751
McMaster University Medical Centre	642
Winnipeg	
Health Sciences Centre Winnipeg	1697
Edmonton	
Walter C. MacKenzie Health Sciences Centre	1580
London	
Victoria Hospital	747
United States	
Cleveland	
Cleveland Clinic	1248
St. Louis	
Washington University School of Medicine	141
Asia	(10,005)
China	
Hong Kong	
Prince of Wales Hospital	4413
India	
Bangalore	
St. John's Medical College Hospital	1996
Ludhiana	
Christian Medical College	1549
Malaysia	

Continent, country, city, centre	Participants (n=40,004)
Kuala Lumpur	
University Malaya Medical Centre	2047
Europe	(9671)
United Kingdom	
London	
Barts And The London	2007
University College Hospital	880
Leeds	
Leeds Teaching Hospitals	733
Liverpool	
Royal Liverpool University Hospital	722
Spain	
Barcelona	
Hospital de Sant Pau	1985
Madrid	
Hospital Gregorio Maranon	1764
Poland	
Krakow	
Jagiellonian University Medical College	982
France	
Paris	
Pitie-Salpetriere Hospital	598
South America	(6063)
Brazil	
São Paulo	
Hospital do Coracao	1503
Porto Alegre	
Hospital de Clinicas de Porto Alegre	1001
Colombia	
Bucaramanga	
Hospital Universitario de Santander	1392
Bogota	
Foundation CardioInfanil	628
Peru	
Lima	
Hospital Nacional Cayetano Heredia	1539
Africa	(1489)
South Africa	
Durban	
Inkosi Albert Luthuli Hospital	1489
Australia	(1083)
Australia	
Sydney	
Westmead Hospital	1083

Table 4: Variables used in logistic regression model

Variable	Type	Result
Postoperative clinically important hypotension	Binary	Yes/No
Surgical variables		
Pneumonectomy	Binary	Yes/No
Complex visceral resection	Binary	Yes/No
Major hip/pelvic surgery	Binary	Yes/No
Knee arthroplasty	Binary	Yes/No
Lobectomy	Binary	Yes/No
Radical prostatectomy	Binary	Yes/No
Aorto-iliac reconstructive surgery	Binary	Yes/No
Stomach surgery	Binary	Yes/No
Other thoracic surgery	Binary	Yes/No
Cytoreductive surgery	Binary	Yes/No
Visceral resection	Binary	Yes/No
Radical hysterectomy	Binary	Yes/No
TURP	Binary	Yes/No
Above knee amputation	Binary	Yes/No
Craniotomy	Binary	Yes/No
Head and neck surgery	Binary	Yes/No
EVAR	Binary	Yes/No
Intra-abdominal surgery	Binary	Yes/No
Thoracic aorta reconstructive surgery	Binary	Yes/No
Hysterectomy	Binary	Yes/No
Peripheral vascular reconstruction	Binary	Yes/No
Cerebrovascular surgery	Binary	Yes/No
Internal fixation of femur	Binary	Yes/No
Major spine surgery	Binary	Yes/No
Lower leg amputation	Binary	Yes/No
Open vs endoscopic surgery	Binary	Yes/No
Timing of surgery	Categorical	>72 hours 24-72 hours <24 hours
Patient characteristics		
Age	Continuous	years
Male sex	Binary	Yes/No
History of smoking	Binary	Yes/No
Living in a nursing home	Binary	Yes/No
Need assistance with ADL	Binary	Yes/No
History or current atrial fibrillation	Binary	Yes/No
History of CHF	Binary	Yes/No
History of cardiac arrest	Binary	Yes/No
History of DVT/PE	Binary	Yes/No
History of cerebral vascular events	Binary	Yes/No
History of peripheral vascular disease	Binary	Yes/No
History of hypertension	Binary	Yes/No
Coronary artery disease	Ordinal	No CAD History of CAD Recent high-risk CAD
History of aortic stenosis	Binary	Yes/No
History of COPD	Binary	Yes/No

History of diabetes mellitus	Binary	Yes/No
Preoperative hemodynamics		
Preoperative systolic BP	Continuous	mm Hg
Preoperative diastolic BP	Continuous	mm Hg
Preoperative heart rate	Continuous	beats per min
Preoperative laboratory values		
Hemoglobin	Continuous	g L^{-1}
eGFR	Continuous	mL min^{-1}
Intraoperative variables		
Intraoperative hypotension (SBP <90 mm Hg)	Binary	Yes/No
Intraoperative Tachycardia (HR >100 bpm)	Binary	Yes/No
Intraoperative Bradycardia (HR <55 bpm)	Binary	Yes/No
Duration of Surgery	Continuous	Minutes

ADL: activities of daily living; BPM: beats per minute; CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; eGFR: estimated glomerular filtration rate; EVAR: endovascular aneurysm repair; HR: heart rate; PE: pulmonary embolism; SBP: systolic blood pressure; TURP: transurethral resection of the prostate.

Figure 1: Patient flow chart

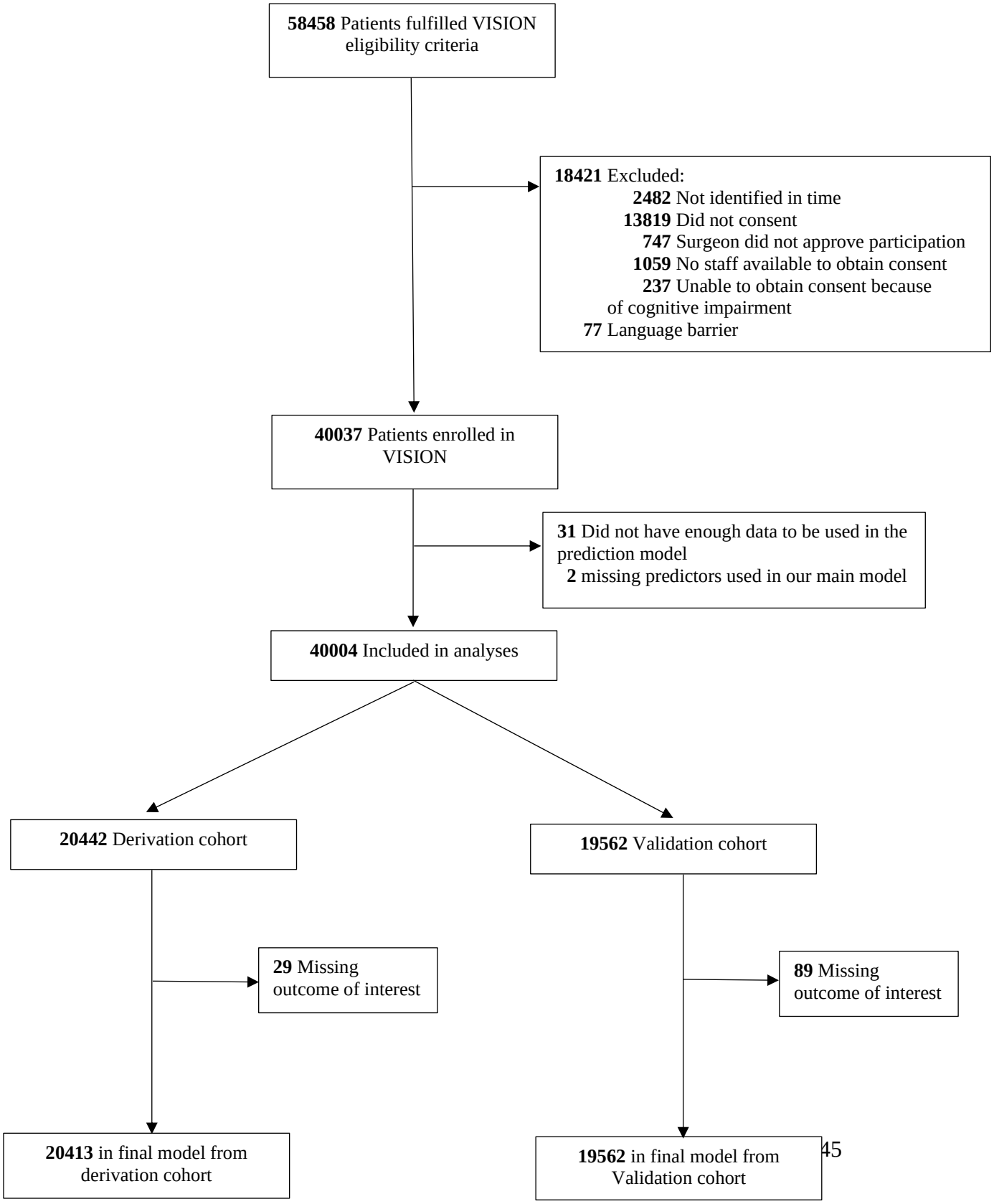


Table 5: Patient characteristics

	All patients N=40004	Derivation cohort N=20442	Validation cohort N=19562	p-value*
Age, mean (SD)	64.0 (11.3)	64.9 (11.6)	63.1 (10.9)	<0.001
Males	20127 (50.3)	10113 (49.5)	10014 (51.2)	0.001
History of: n (%)				
Smoking	18643 (46.8) N=39838	9769 (47.8) N=20435	8874 (45.7) N=19403	<0.001
Diabetes	8332 (20.9) N=39905	3939 (19.3) N=20440	4393 (22.6) N=19465	<0.001
Hypertension	20152 (50.5) N=39917	10255 (50.2) N=20439	9897 (50.8) N=19478	0.203
Living in a nursing home	574 (1.4) N=39882	342 (1.7)	232 (1.2) N=19440	<0.001
Need assistance with ADL	2130 (5.3) N=39869	896 (4.4) N=20440	1234 (6.4) N=19429	<0.001
History or current atrial fibrillation	1262 (3.2) N=39827	668 (3.3) N=20428	594 (3.1) N=19399	0.236
CHF	1424 (3.6) N=39870	702 (3.4) N=20438	722 (3.7) N=19432	0.131
CAD	5159 (12.9) N=39876	2560 (12.5) N=20435	2599 (13.4) N=19441	0.012
High risk CAD	384 (1.0)	209 (1.0)	175 (0.9)	0.190
Coronary revascularization over 1 year	2923 (7.3) N=39869	1486 (7.3) N=20441	1437 (7.4) N=19428	0.627
Coronary revascularization within 1 year	564 (1.4) N=39861	310 (1.5) N=20437	254 (1.3) N=19424	0.077
Cardiac arrest	235 (0.6) N=39868	103 (0.5) N=20437	132 (0.7) N=19431	0.022
Aortic Stenosis	387 (1.0) N=39861	254 (1.2) N=20433	133 (0.7) N=19428	<0.001
Peripheral vascular disease	3203 (8.0)	1153 (5.6)	2050 (10.5)	<0.001
Cerebral vascular event	2582 (6.5)	1407 (6.9)	1175 (6.0)	<0.001
DVT/PE	1312 (3.3) N=39865	653 (3.2) N=20439	659 (3.4) N=19426	0.269
COPD	3165 (7.9)	1575 (7.7)	1590 (8.1)	0.117
OSA	1932 (4.9) N=39855	982 (4.8) N=20430	950 (4.9) N=19425	0.697
Cancer (any of active cancer, surgery for cancer, or metastatic disease)	9832 (24.6)	5287 (25.9)	4545 (23.2) N=19562	<0.001
Preoperative vital signs				
Preoperative HR, mean (SD)	77.4 (14.5) N=39716	77.6 (12.6) N=20360	77.2 (14.5) N=19356	0.019
Preoperative SBP, mean (SD)	139.7 (23.3)	141.0 (24.3) N=20399	138.3 (22.2) N=19414	<0.001
Preoperative DBP, mean (SD)	78.6 (13.1)	79.1 (13.5) N=20311	78.1 (12.6) N=19393	<0.001
Preoperative laboratory tests				
Preoperative eGFR, mean (SD)	79.6 (24.3) N=37290	78.8 (23.4) N=19022	80.6 (25.1) N=18268	<0.001

Preoperative Hemoglobin, mean (SD)	130.1 (19.3) N=38617	130.5 (19.0) N=19724	129.8 (19.6) N=18893	<0.001
Surgery, n (%)				
Vascular without EVAR	2352 (5.9)	846 (4.14)	1506 (7.7)	<0.001
EVAR	302 (0.8)	123 (0.6)	179 (0.9)	<0.001
General	7950 (19.9)	4189 (20.5)	3761 (19.2)	0.002
Thoracic	1165 (2.9)	810 (4.0)	355 (1.8)	<0.001
Major urology/gynecology	4827 (12.1)	2466 (12.1)	2361 (12.1)	0.986
Major orthopedic	6982 (17.5)	4151 (20.3)	2831 (14.5)	<0.001
Major neurosurgery	2341 (5.9)	1102 (5.4)	1239 (6.3)	<0.001
Low risk surgeries	15308 (38.3)	7721 (37.8)	7587 (38.8)	0.037
Open surgery, n (%)	31288 (78.3) N=39978	15966 (78.1) N=20439	15322 (78.4) N=19539	0.464
Timing of surgery, n (%)				<0.001
>72 hours	35815 (89.5)	17820 (87.2)	17995 (92.0)	
24-72 hours	3076 (7.7)	2081 (10.2)	995 (5.1)	
<24 hours	1113 (2.8)	541 (2.7)	572 (2.9)	
Anesthesia				
General	29073 (72.7) N=39976	14231 (69.6)	14842 (76.0) N=19534	<0.001
Spinal	9811 (24.5) N=39971	6053 (29.6)	3758 (19.2) N=19529	<0.001
Epidural	4489 (11.2) N=39968	2213 (10.8) N=20441	2276 (11.7) N=19527	0.009
Nerve block	2761 (6.9) N=39971	982 (4.8)	1779 (9.1) N=19529	<0.001
Intraoperative hypotension (SBP <90), n (%)	18487 (47.0) N=39317	8734 (43.6) N=20026	9753 (50.6) N=19291	<0.001
Postoperative hypotension (SBP <90), n (%)	8733 (21.9) N=39886	4721 (23.1) N=20413	4012 (20.6) N=19473	<0.001

Table with clinical characteristics of patients in the derivation cohort versus the validation cohort. Results expressed as n (%) unless otherwise stated. ADL: activities of daily living; CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; eGFR: estimated glomerular filtration rate; EVAR: endovascular aneurysm repair; HR: heart rate; OSA: obstructive sleep apnea; PE: pulmonary embolism; SBP: systolic blood pressure; SD: standard deviation; TURP: transurethral resection of the prostate.

*t-test for heart rate, SBP, and DBP; chi-squared test for all other variables

Table 6: Timing of postoperative CIH

Timing	**Patients with clinically important hypotension**	**95% CI***
In PACU	1632 (4.4) N=36967	4.2-4.6
Day of surgery post-PACU	1379 (3.7) N=37178	3.5-3.9
Day 1 after surgery	2239 (5.7) N=39380	5.5-5.9
Day 2 after surgery	841 (2.5) N=34156	2.3-2.6
Day 3 after surgery	383 (1.3) N=30148	1.1-1.4
Later than day 3 after surgery	668 (2.5) N=26863	2.3-2.7
In PACU until discharged	4959 (12.4) N=39886	12.1-12.8

Results expressed as n (%) unless otherwise stated. CI: confidence interval; PACU: post-anesthetic care unit.

*95% confidence interval calculated using normal approximation

Table 7: Model using categorical variables

	Multivariable analysis, N=18676	
Independent variables	Adjusted OR (95% CI)	p-value
Type of Surgery		
Pneumonectomy	5.10 (1.92-13.51)	0.001
Complex visceral resection	4.24 (3.42-5.25)	<0.001
Major hip/pelvic surgery	3.71 (3.16-4.36)	<0.001
Lobectomy	3.55 (2.60-4.85)	<0.001
Knee arthroplasty	3.32 (2.82-3.89)	<0.001
Radical prostatectomy	3.12 (2.21-4.41)	<0.001
Aorto-iliac reconstructive surgery	3.12 (2.19-4.41)	<0.001
Stomach surgery	2.97 (2.50-3.53)	<0.001
Other thoracic surgery	2.89 (2.17-3.87)	<0.001
Cytoreductive surgery	2.60 (1.75-3.88)	<0.001
Visceral resection	2.43 (1.86-3.16)	<0.001
Radical hysterectomy	2.21 (1.43-3.42)	<0.001
TURP	1.92 (1.34-2.73)	<0.001
Major spine surgery	1.82 (1.36-2.44)	<0.001
Above knee amputation	1.74 (0.89-3.40)	0.106
Head and neck surgery	1.73 (1.18-2.56)	0.005
Craniotomy	1.72 (1.26-2.36)	0.001
Intra-abdominal surgery	1.70 (1.44-2.01)	<0.001
Internal fixation of femur	1.51 (1.08-2.12)	0.015
Hysterectomy	1.50 (1.16-1.94)	0.002
EVAR	1.42 (0.70-2.86)	0.330
Peripheral vascular reconstruction	1.42 (0.99-2.07)	0.057
Thoracic aorta reconstructive surgery	1.27 (0.54-2.98)	0.579
Cerebrovascular surgery	1.18 (0.71-1.94)	0.527
Lower leg amputation	0.99 (0.44-2.22)	0.984
Open vs Endoscopic surgery	2.02 (1.73-2.35)	<0.001
Timing of surgery		
>72 hours	Reference	
24-72 hours	0.69 (0.58-0.83)	<0.001
<24 hours	1.27 (0.97-1.68)	0.082
Patient characteristics		
Age		
45-50	Reference	
50-65	1.22 (1.00-1.48)	0.050
65-80	1.36 (1.10-1.68)	0.004
≥80	1.35 (1.05-1.72)	0.017
Male sex	0.76 (0.69-0.85)	<0.001
History of smoking	1.27 (1.15-1.40)	<0.001
Need assistance with ADL	1.37 (1.13-1.67)	0.002
History or current atrial fibrillation	1.42 (1.19-1.68)	<0.001
Coronary Artery disease		
No CAD	Reference	
History of CAD	1.25 (1.08-1.43)	0.002
Recent high-risk CAD	1.51 (1.03-2.19)	0.031
History of aortic stenosis	1.88 (1.38-2.56)	<0.001
History of COPD	1.39 (1.19-1.62)	<0.001
History of diabetes mellitus	0.86 (0.76-0.97)	0.016

Preoperative hemodynamics		
Preoperative SBP		
<110	2.47 (2.06-2.98)	<0.001
110-140	1.49 (1.33-1.67)	<0.001
140-175	Reference	
>175	0.78 (0.64-0.94)	0.009
Preoperative DBP		
<60	1.51 (1.24-1.83)	<0.001
60-80	1.31 (1.17-1.46)	<0.001
80-100	Reference	
>100	0.90 (0.72-1.13)	0.389
Preoperative heart rate		
<60	Reference	
60-80	1.19 (0.99-1.43)	0.063
80-100	1.33 (1.10-1.61)	0.004
>100	1.96 (1.55-2.48)	<0.001
Preoperative laboratory values		
Hemoglobin (g L^{-1})		
>150	Reference	
130-150	1.13 (0.97-1.32)	0.115
100-130	1.27 (1.08-1.49)	0.003
<100	1.21 (0.95-1.51)	0.120
eGFR		
>100	Reference	
80-100	1.03 (0.88-1.21)	0.684
45-80	1.14 (0.96-1.34)	0.127
<45	1.28 (1.03-1.58)	0.023

Multivariable logistic regression using categorical variables. ADL: activities of daily living; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; EVAR: endovascular aneurysm repair; OR: odds ratio; SBP: systolic blood pressure; TURP: transurethral resection of the prostate.

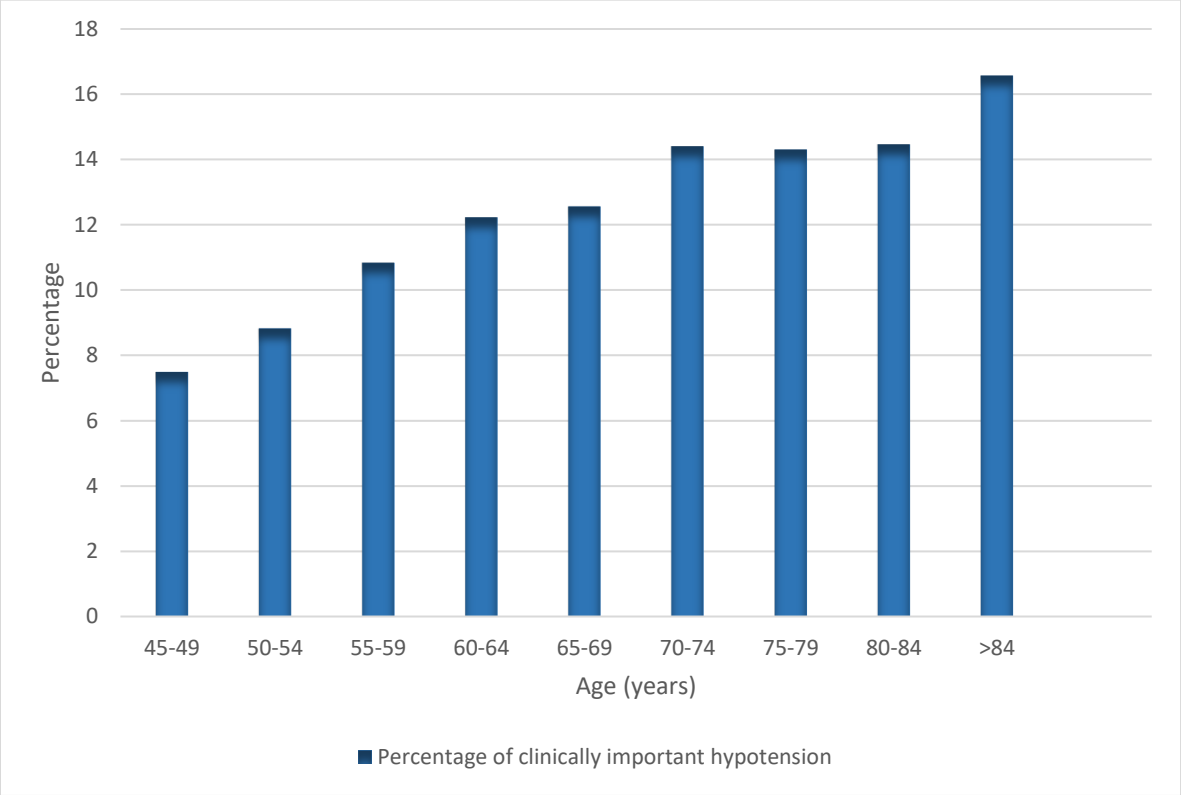
Table 8: Variance inflation factor of predictors included in main model

Variable	VIF
EVAR	1.03
Thoracic aorta reconstructive surgery	1.01
Aorto-iliac reconstructive surgery	1.05
Peripheral vascular reconstruction	1.07
Cerebrovascular surgery	1.05
Complex visceral resection	1.04
Stomach surgery	1.09
Intra-abdominal surgery	1.14
Head and neck surgery	1.03
Pneumonectomy	1.00
Lobectomy	1.05
Other thoracic surgery	1.05
Visceral resection	1.03
Cytoreductive surgery	1.03
Hysterectomy	1.11

Radical hysterectomy	1.03
Radical prostatectomy	1.05
TURP	1.17
Major hip/pelvic surgery	1.24
Internal fixation of femur	1.14
Knee arthroplasty	1.26
Above knee amputation	1.03
Lower leg amputation	1.03
Craniotomy	1.07
Major spine surgery	1.07
Open surgery	1.28
Timing of surgery	
24-72 hours	1.14
< 24 hours	1.03
Age	1.63
Male sex	1.30
History of smoking	1.18
Need assistance with ADL	1.08
History or current atrial fibrillation	1.08
History of COPD	1.09
History of diabetes mellitus	1.07
Coronary Artery disease	
History of CAD	1.12
Recent high-risk CAD	1.03
History of aortic stenosis	1.03
Preoperative systolic blood pressure	1.72
Preoperative diastolic blood pressure	1.70
Preoperative HR	1.13
Preoperative eGFR	1.35
Preoperative hemoglobin	1.24
Mean VIF	**1.14**

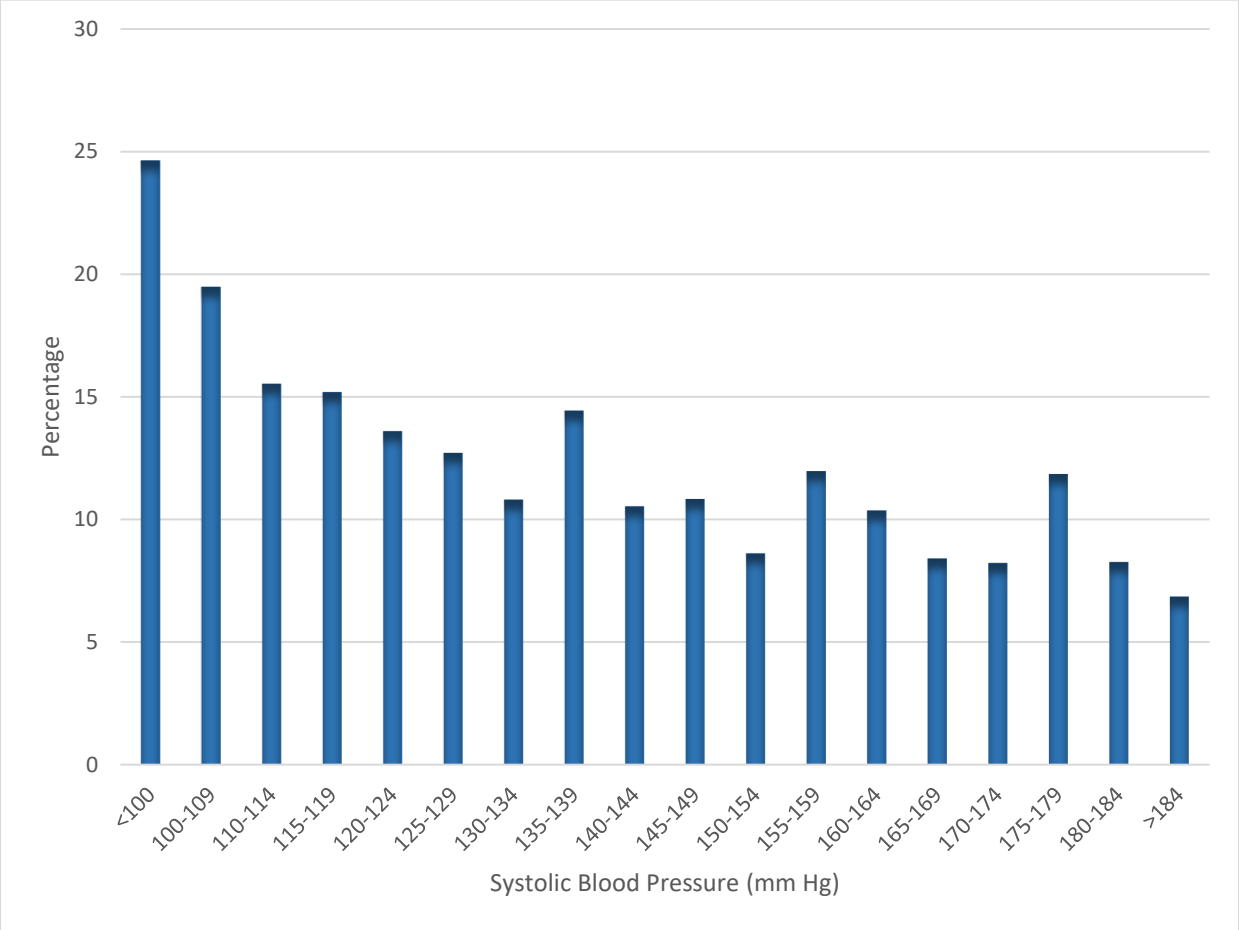
ADL: activities of daily living; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; EVAR: endovascular aneurysm repair; HR: heart rate; VIF: variance inflation factor

Figure 2: Postoperative CIH by age



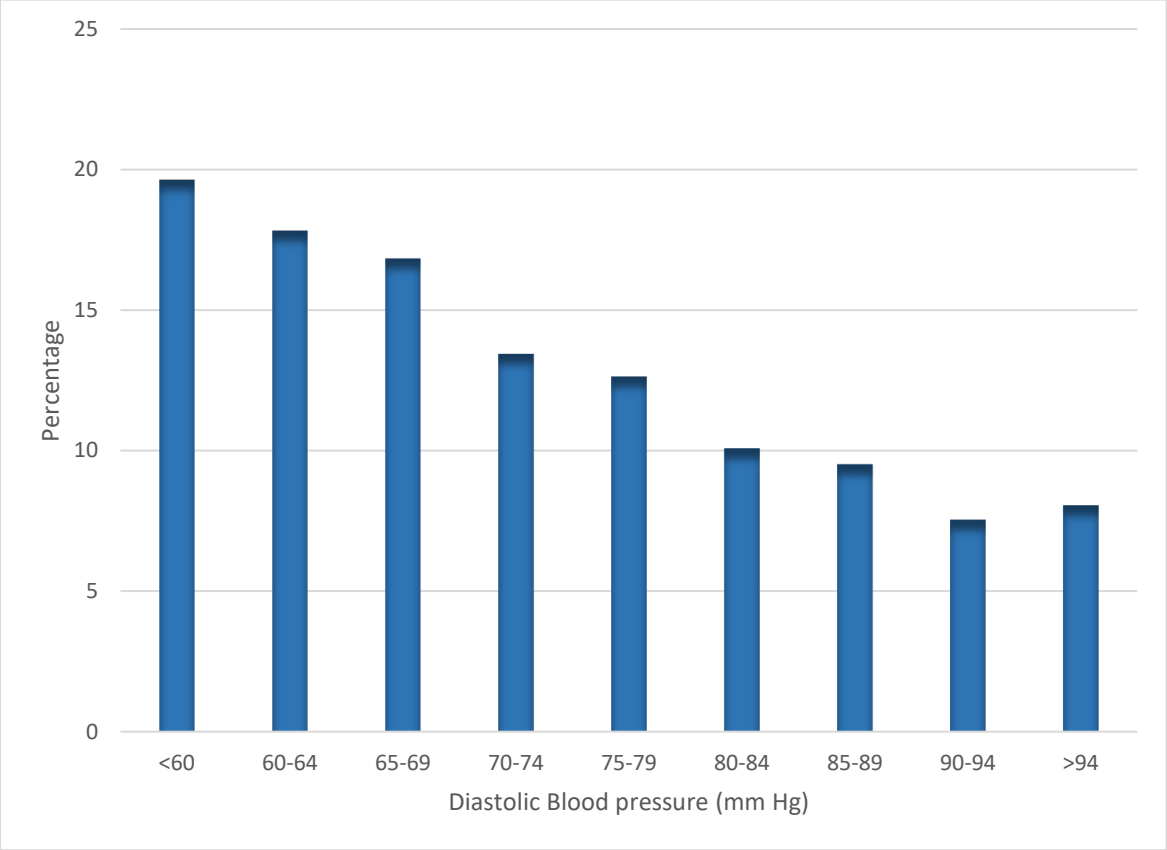
Bar graph illustrating the relationship between age and postoperative clinically important hypotension. Y-axis: percentage of postoperative clinically important hypotension. X-axis: age in 4-year intervals.

Figure 3: Postoperative CIH by systolic blood pressure



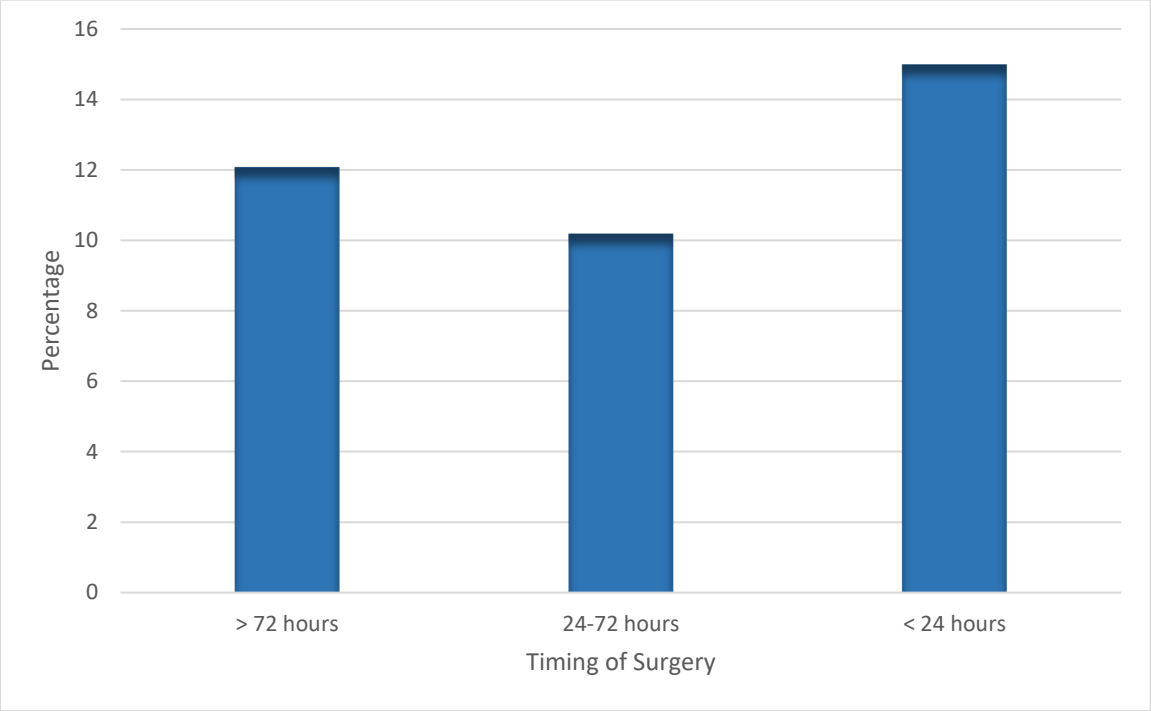
Bar graph illustrating the relationship between preoperative systolic blood pressure and postoperative clinically important hypotension. Y-axis: percentage of postoperative clinically important hypotension. X-axis: preoperative systolic blood pressure.

Figure 4: Postoperative CIH by diastolic blood pressure



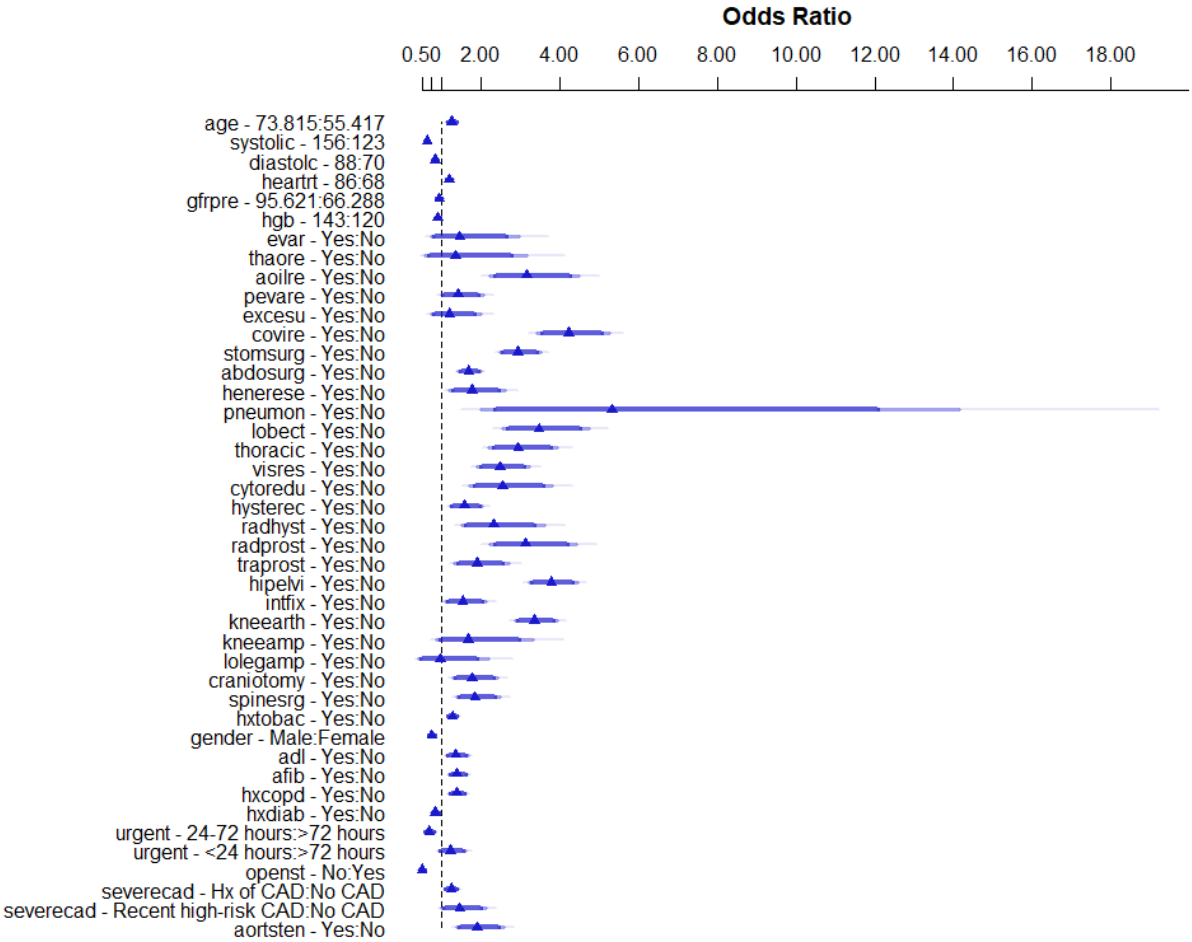
Bar graph illustrating the relationship between preoperative diastolic blood pressure and postoperative clinically important hypotension. Y-axis: percentage of postoperative clinically important hypotension. X-axis: diastolic blood pressure in 4 mm Hg intervals.

Figure 5: Postoperative CIH by timing of surgery



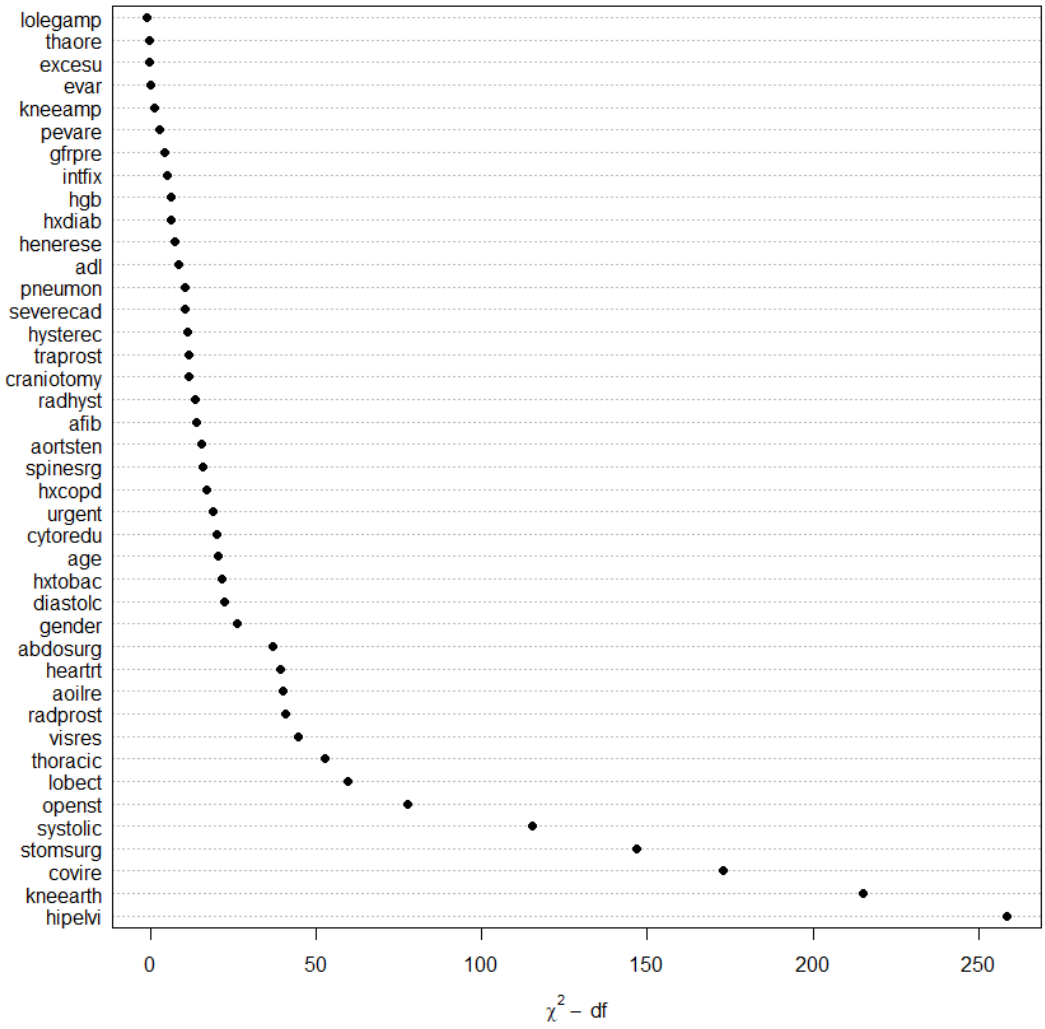
Bar graph illustrating the relationship between the timing of surgery and postoperative clinically important hypotension. Y-axis: percentage of postoperative clinically important hypotension. X-axis: the timing of surgery.

Figure 6: Odds ratio and 95% confidence interval of predictors



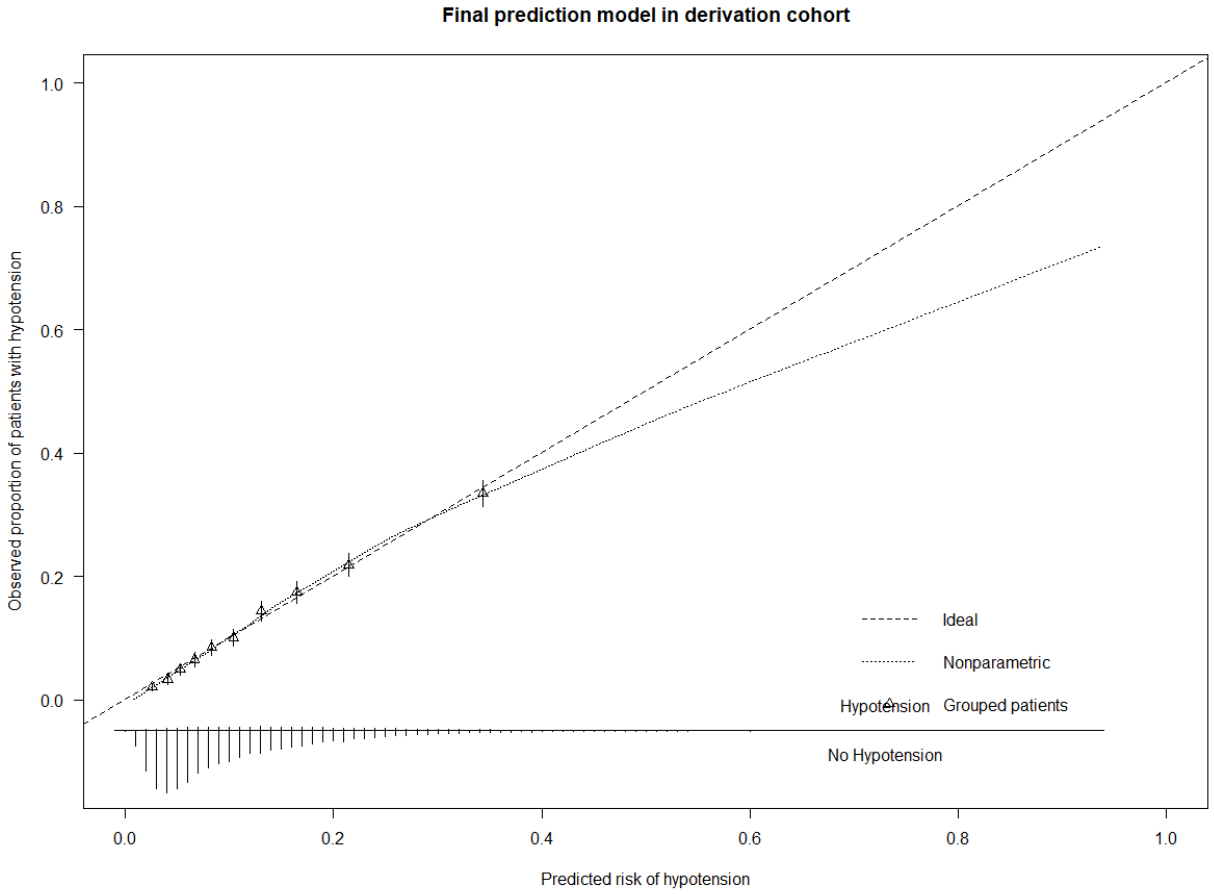
Graphic representation of adjusted odds ratio and 95% confidence interval of predictors in the final model.

Figure 7: Wald test of predictors



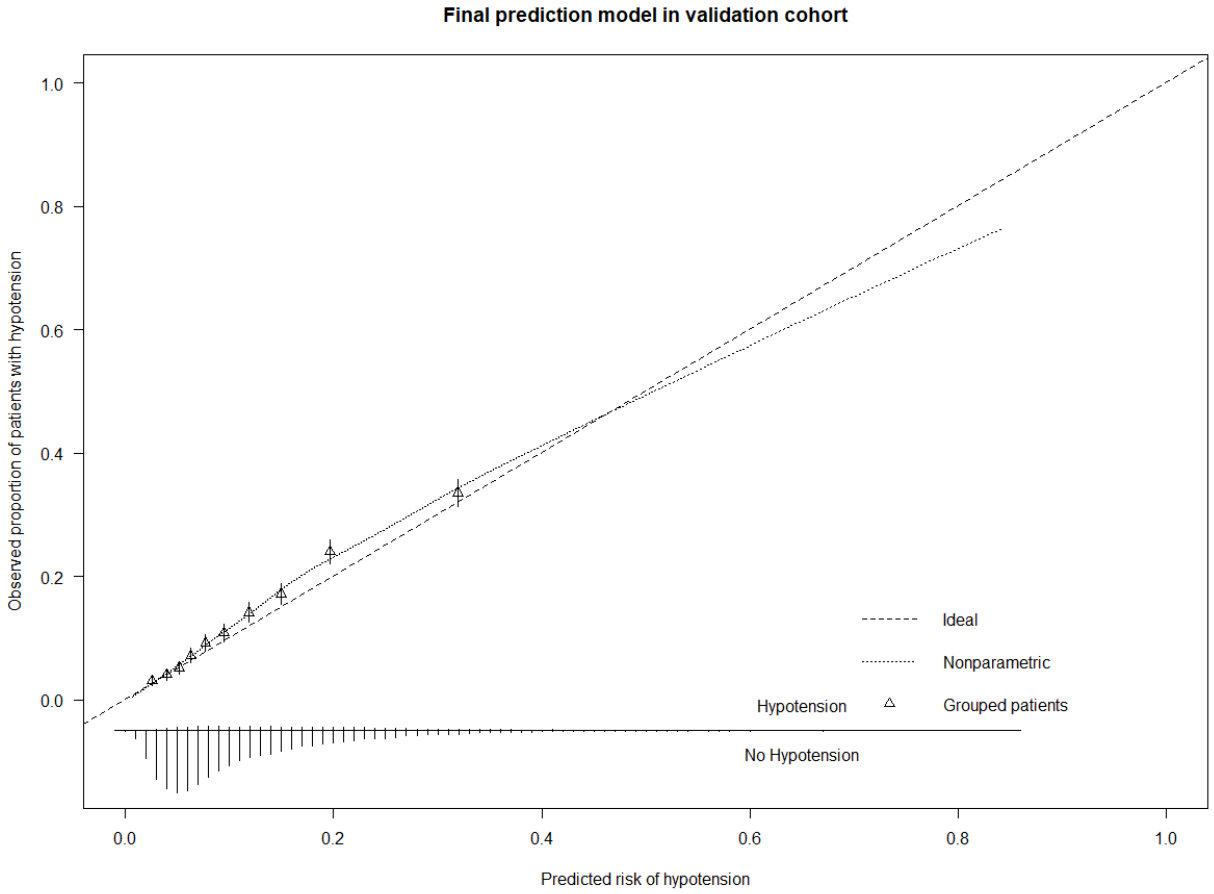
Graphic representation of chi-square using Wald test and degrees of freedom for each predictor included in the final model.

Figure 8: Calibration plot of final model (1)



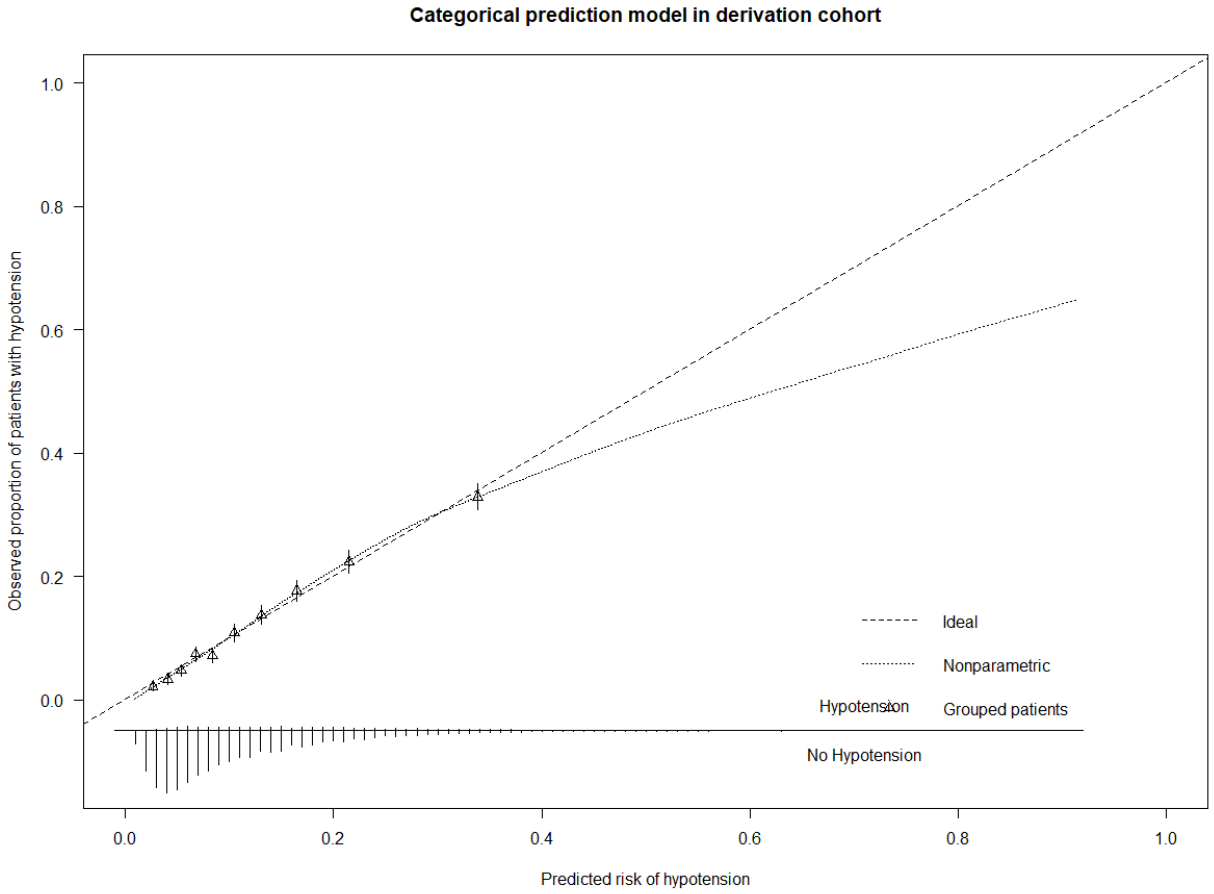
Calibration plot of final clinical prediction model using 41 predictors applied to derivation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients. Nonparametric: line derived from resampling procedure using bootstrapping technique.

Figure 9: Calibration plot of final model (2)



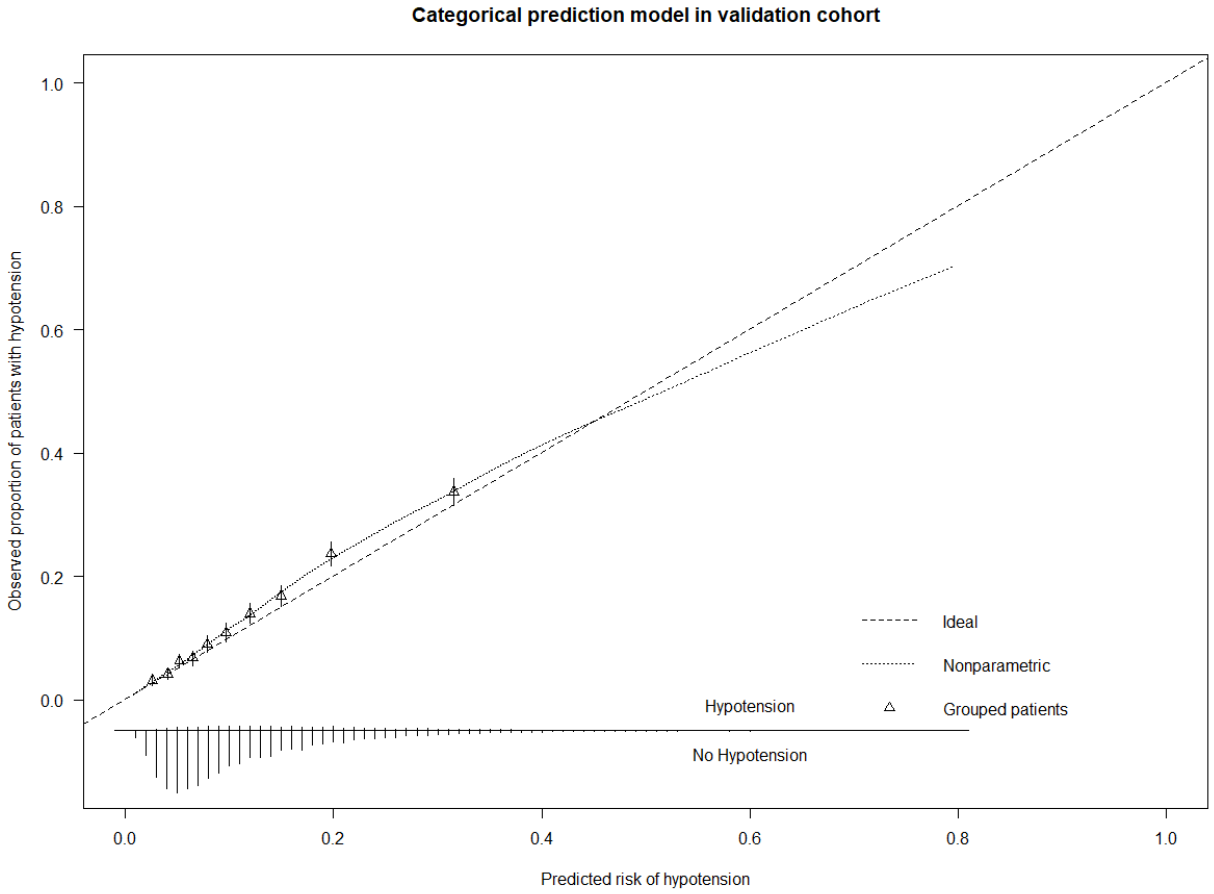
Calibration plot of final clinical prediction model using 41 predictors applied to validation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients.

Figure 10: Calibration plot of model using categorical variables (1)



Calibration plot of the clinical prediction model using categorical variables applied to derivation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients. Nonparametric: line derived from resampling procedure using bootstrapping technique.

Figure 11: Calibration plot of model using categorical variables (2)



Calibration plot of the clinical prediction model using categorical variables applied to validation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients.

Table 9: C-statistics of various models

Prediction model	C-stat original	C-stat optimism corrected	C-stat validation cohort
Main model	0.74	0.73	0.73
Model using categorical variables	0.73	0.73	0.72
Simplified model	0.68	0.68	0.68
Model including intraoperative variables	0.75	0.75	0.73
Model including antihypertensive drugs	0.74	0.73	0.73
Model using imputation	0.74	0.73	0.73

Table 10: Wald test of predictors in the final model

Variable	χ^2	df	p-value	Included in the simplified model
Major hip/pelvic surgery	259.38	1	<0.001	Yes
Knee arthroplasty	215.95	1	<0.001	Yes
Complex visceral resection	173.90	1	<0.001	Yes
Stomach surgery	147.93	1	<0.001	Yes
Preoperative systolic blood pressure	117.08	2	<0.001	Yes
Open surgery	78.68	1	<0.001	Yes
Lobectomy	60.53	1	<0.001	Yes
Other thoracic surgery	53.53	1	<0.001	Yes
Visceral resection	45.62	1	<0.001	Yes
Radical prostatectomy	41.80	1	<0.001	Yes
Aorto-iliac reconstruction	41.00	1	<0.001	Yes
Preoperative heart rate	41.30	2	<0.001	Yes
Intra-abdominal surgery	38.02	1	<0.001	No
Male sex	26.97	1	<0.001	No
Preoperative diastolic blood pressure	24.21	2	<0.001	No

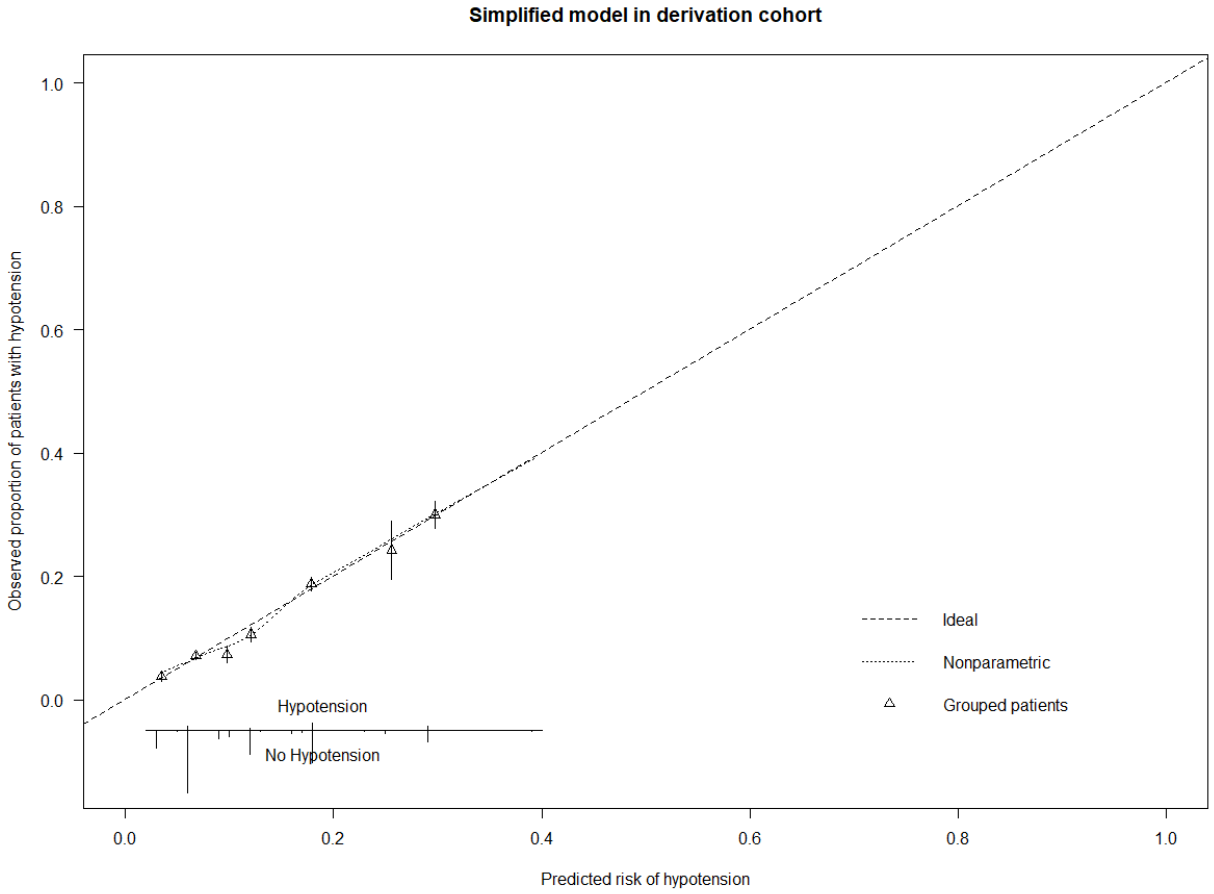
df: degrees of freedom

Table 11: Simplified model with risk scores

Variable	Categories	Odds ratio	Points
High-risk surgery	Yes	2.88	5
	No	1.00	0
Systolic blood pressure <130 mm Hg	Yes	1.85	3
	No	1.00	0
Open surgery	Yes	2.18	4
	No	1.00	0
Preop heart rate >100 bpm	Yes	1.56	2
	No	1.00	0

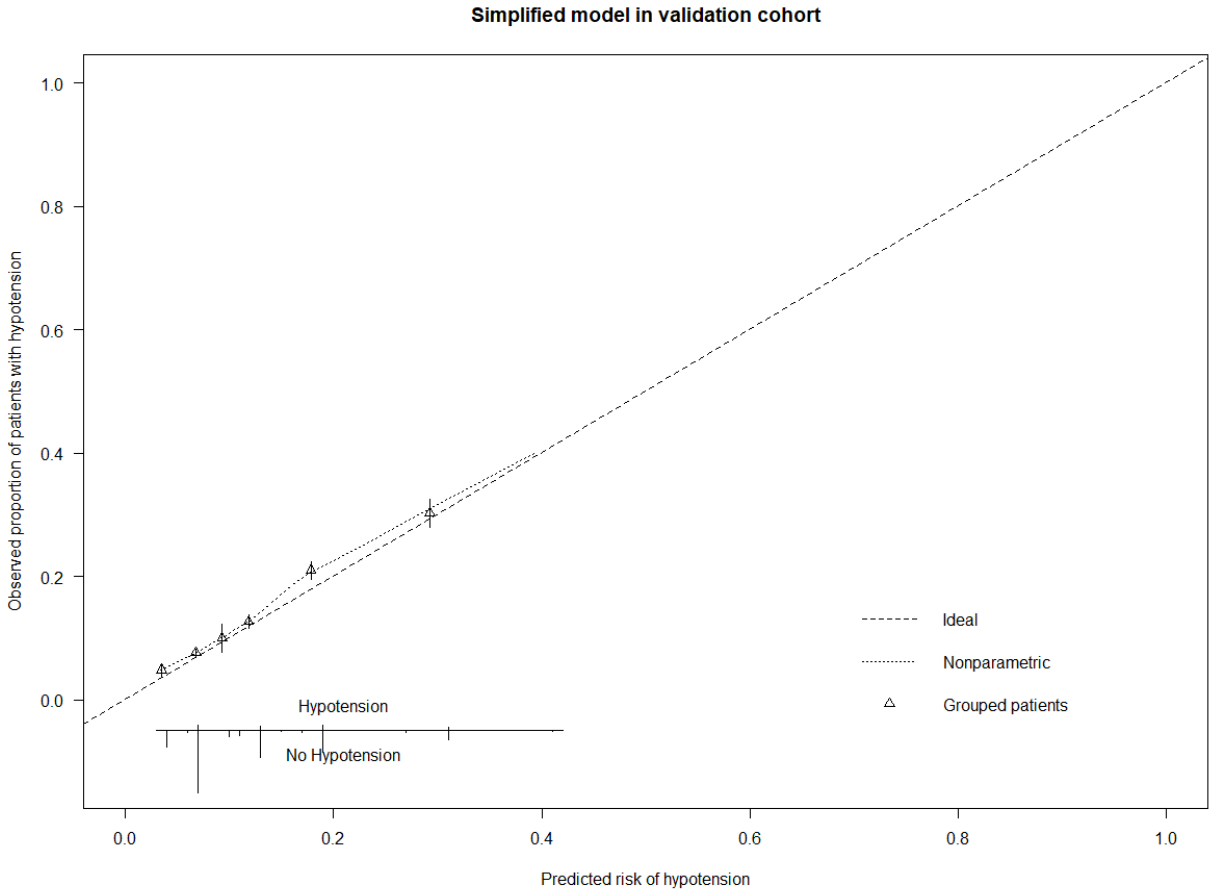
bpm: beats per minute

Figure 12: Calibration plot of simplified model (1)



Calibration plot of the simplified clinical prediction model applied to derivation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients. Nonparametric: line derived from resampling procedure using bootstrapping technique.

Figure 13: Calibration plot of simplified model (2)

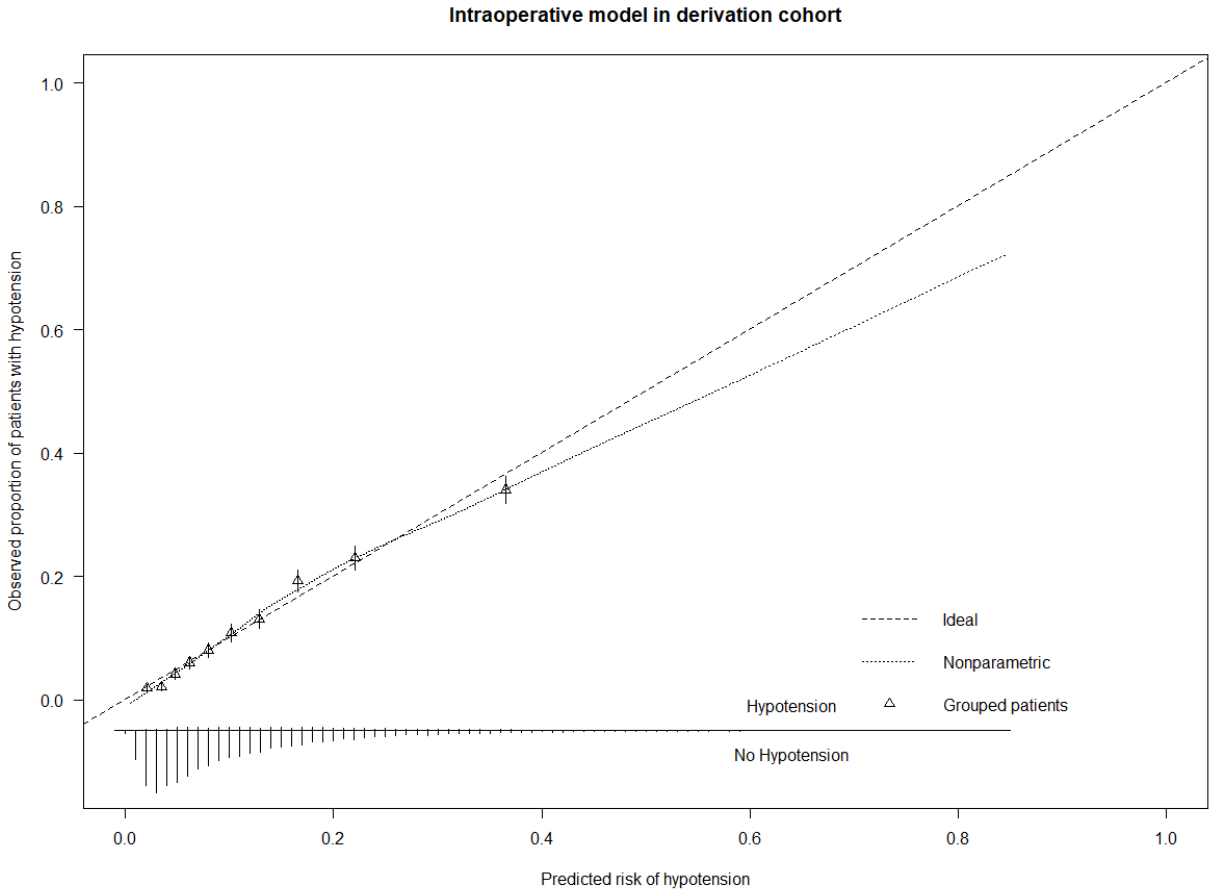


Calibration plot of the simplified clinical prediction model applied to validation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients.

Table 12: Simplified score and predicted probability of postoperative CIH

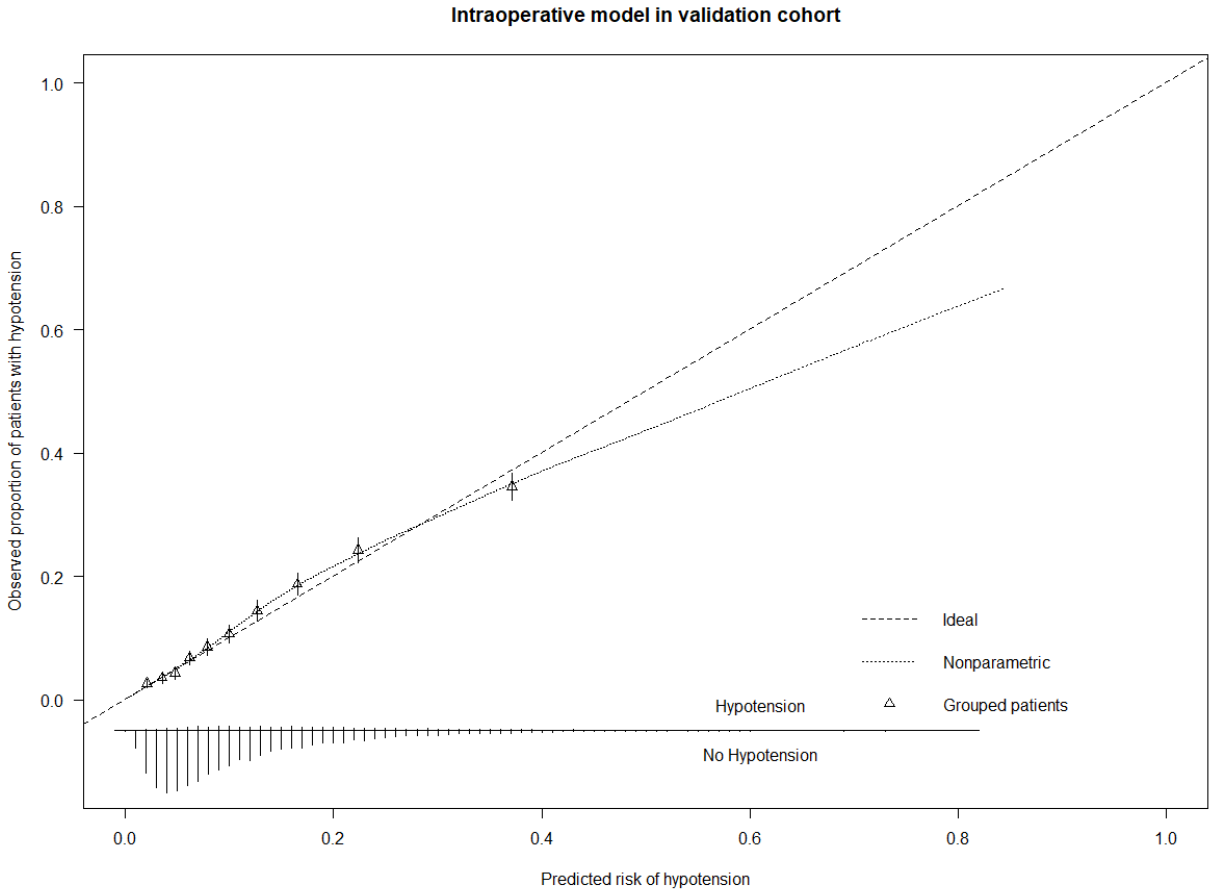
Score	log odds	Probability (%)
0	3.347776	3.4
2	2.947776	5.0
3	2.747776	6.0
4	2.547776	7.3
5	2.347776	8.7
6	2.147776	10.5
7	1.947776	12.5
8	1.747776	14.8
9	1.547776	17.5
10	1.347776	20.6
11	1.147776	24.1
12	0.947776	27.9
13	0.747776	32.1
14	0.547776	36.6

Figure 14: Calibration plot of model including intraoperative variables (1)



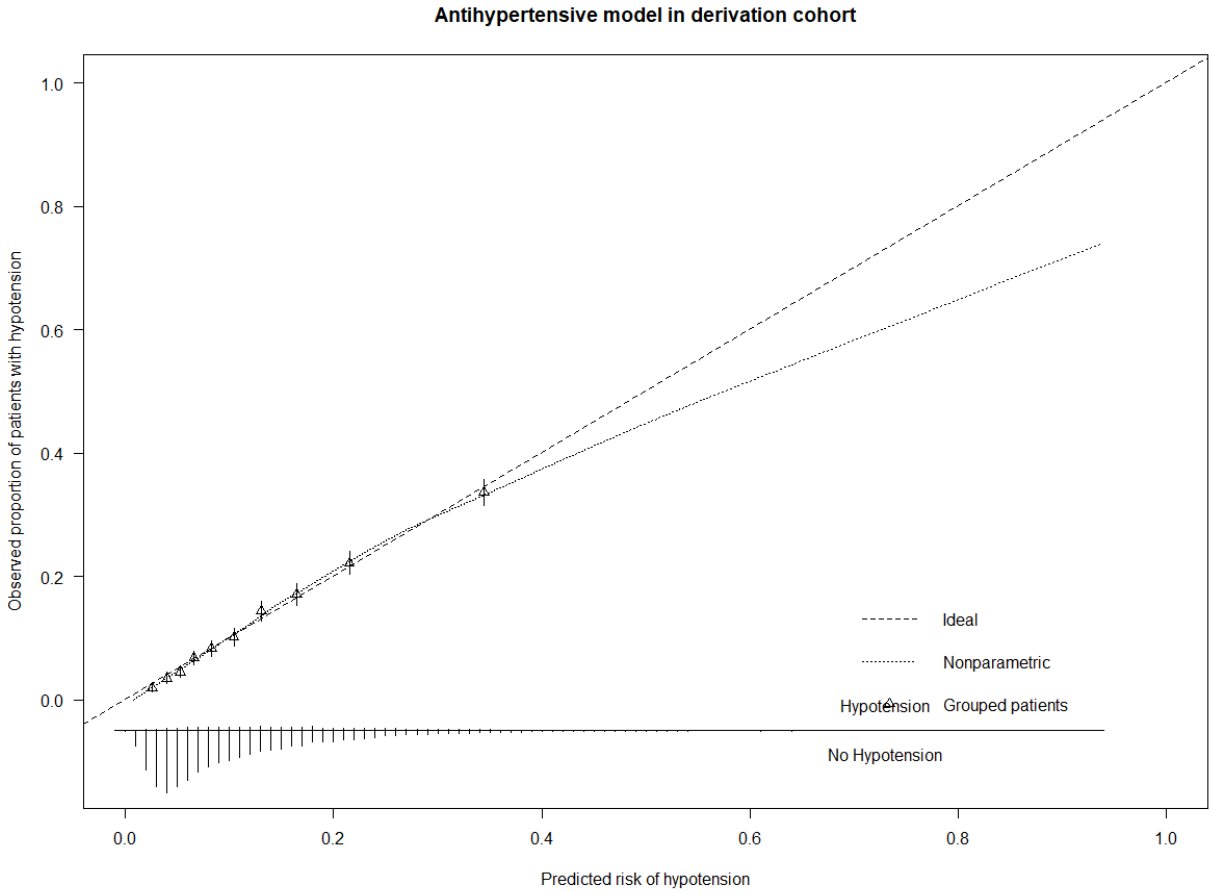
Calibration plot of the clinical prediction model including intraoperative variables applied to derivation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients. Nonparametric: line derived from resampling procedure using bootstrapping technique.

Figure 15: Calibration plot of model including intraoperative variables (2)



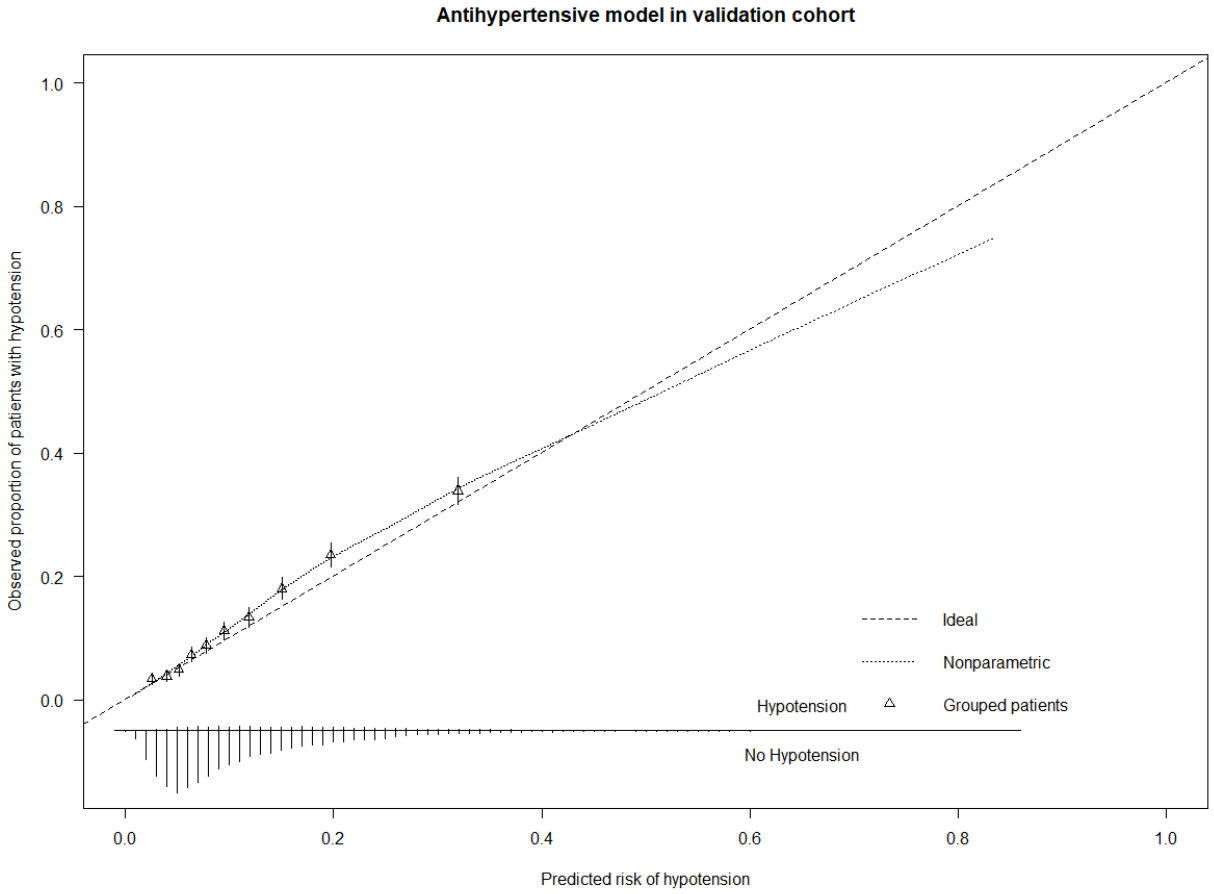
Calibration plot of the clinical prediction model including intraoperative variables applied to validation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients.

Figure 16: Calibration plot of model including antihypertensives (1)



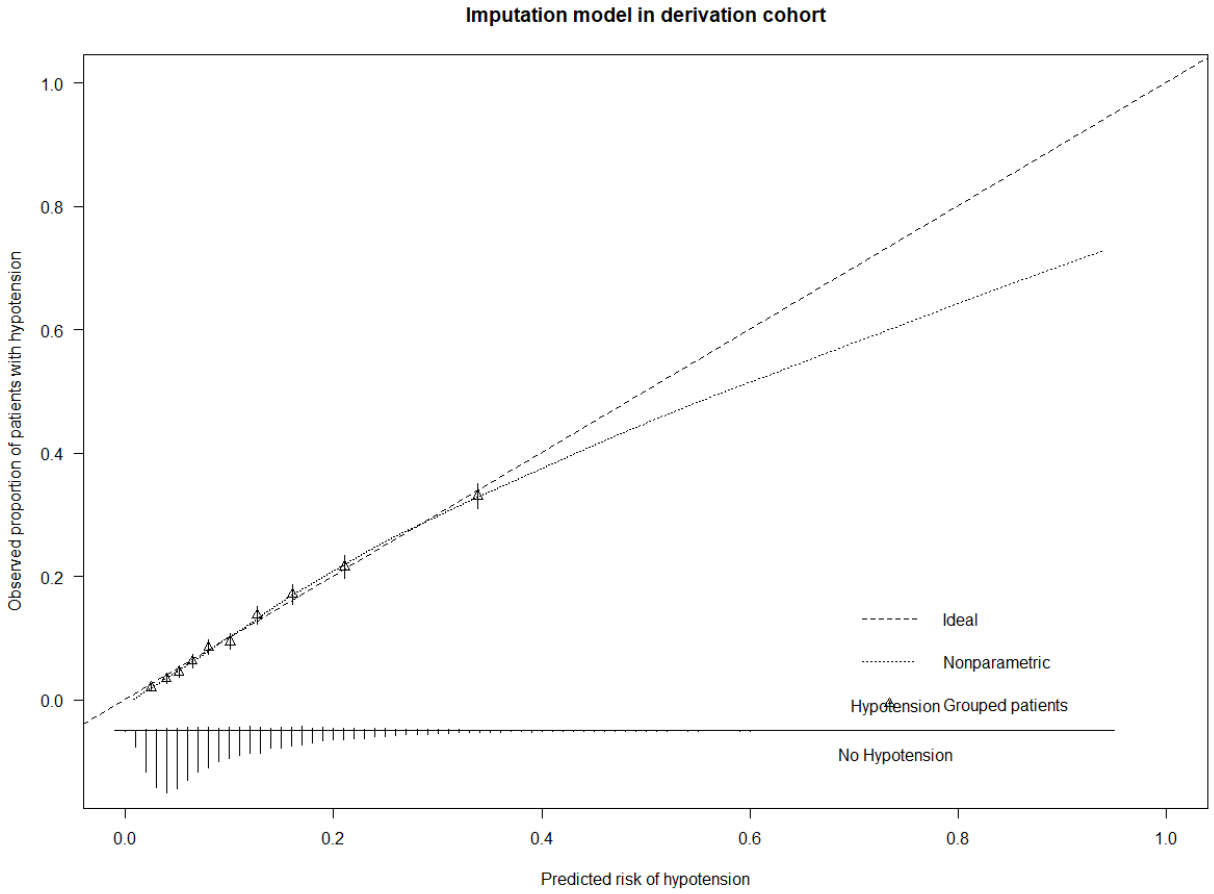
Calibration plot of the clinical prediction model including antihypertensive medication variables applied to derivation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients. Nonparametric: line derived from resampling procedure using bootstrapping technique.

Figure 17: Calibration plot of model including antihypertensives (2)



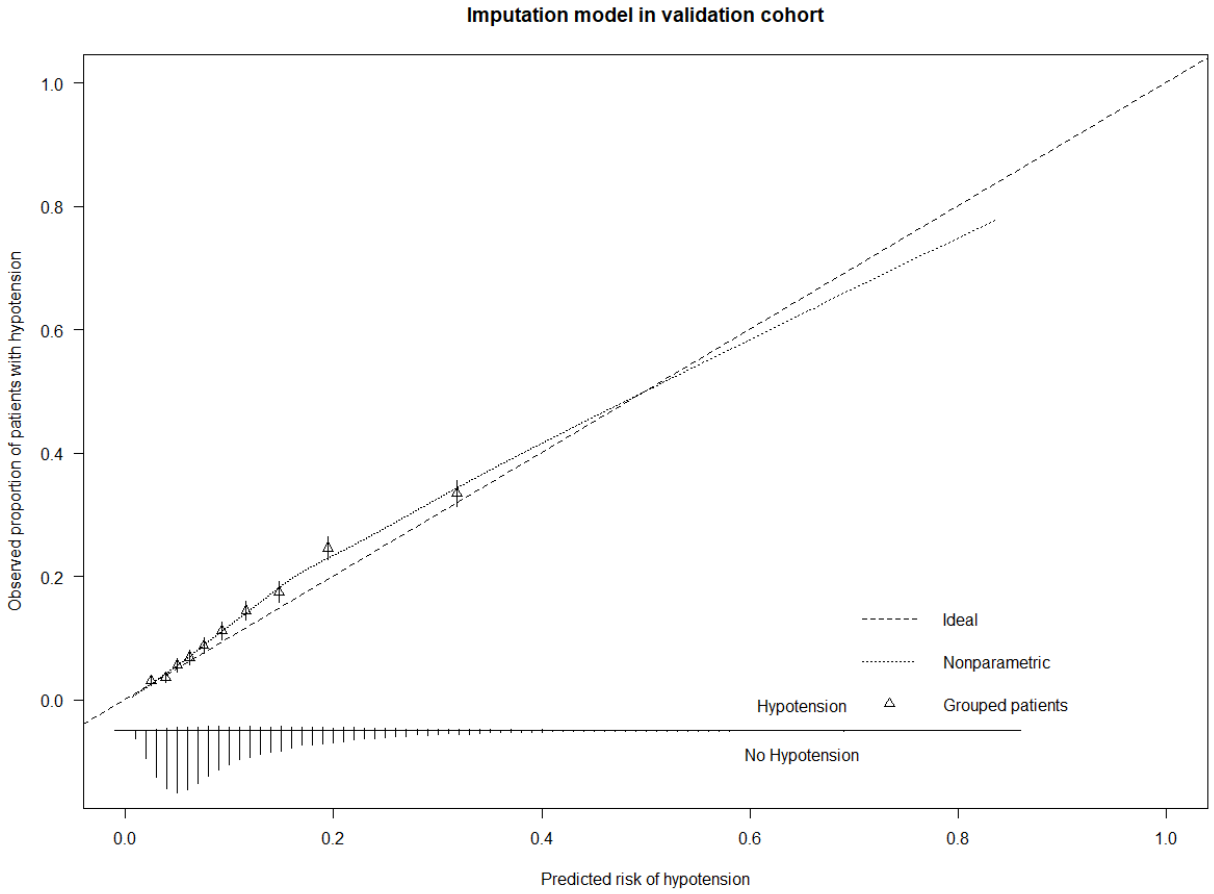
Calibration plot of the clinical prediction model including antihypertensive medication variables applied to validation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients.

Figure 18: Calibration plot of model with imputation (1)



Calibration plot of the clinical prediction model using simple stochastic imputation applied to derivation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients. Nonparametric: line derived from resampling procedure using bootstrapping technique.

Figure 19: Calibration plot of model using imputation (2)



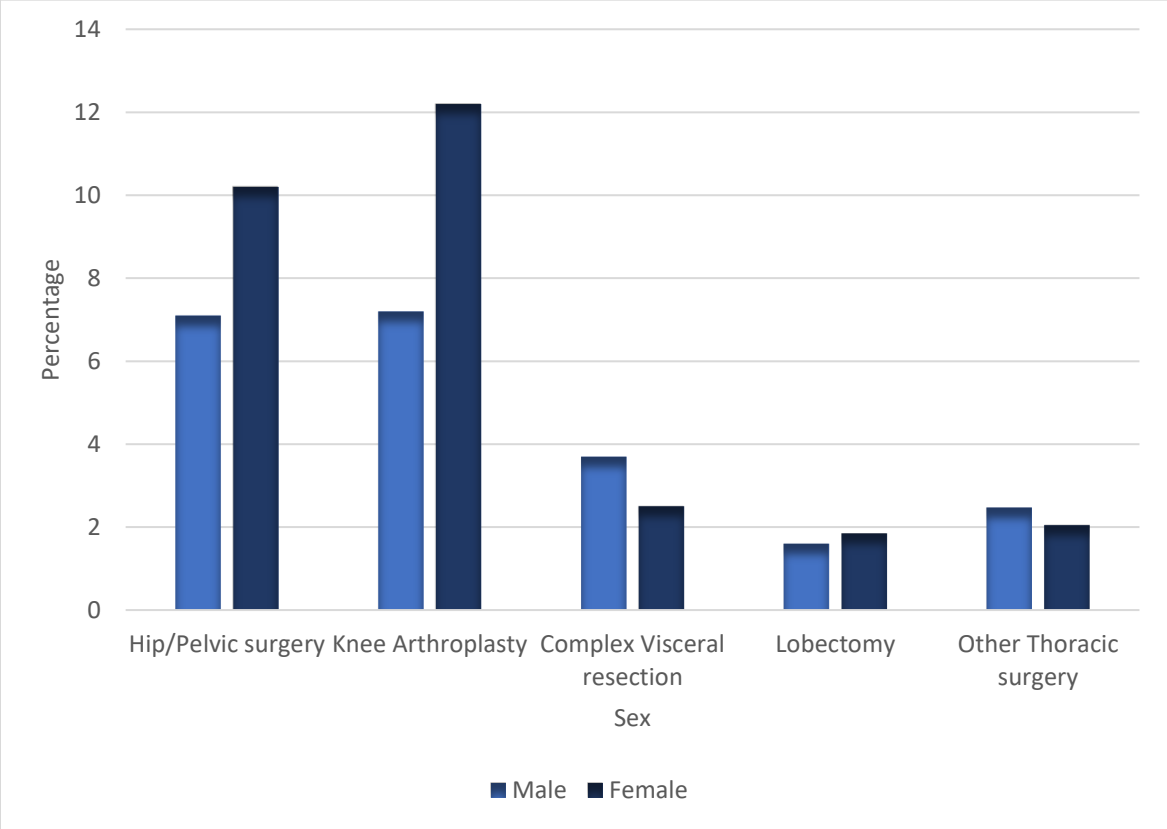
Calibration plot of the clinical prediction model using simple stochastic imputation applied to validation cohort. Y-axis: observed proportion of patients with clinically important postoperative hypotension. X-axis: predicted risk of clinically important postoperative hypotension. Ideal: line to represent perfect prediction risk equal the observed proportion of patients.

Table 13: Missing data in the derivation cohort

Variable	Missing data
Thoracic aortic reconstruction	3
Open surgery	2
History of smoking	7
Patient need assistance with ADL	2
History of aortic stenosis	9
History of coronary artery disease	7
History of hypertension	3
History of diabetes mellitus	2
Preoperative SBP	32
Preoperative DBP	120
Preoperative HR	70
Preoperative eGFR	1418
Preoperative hemoglobin	716

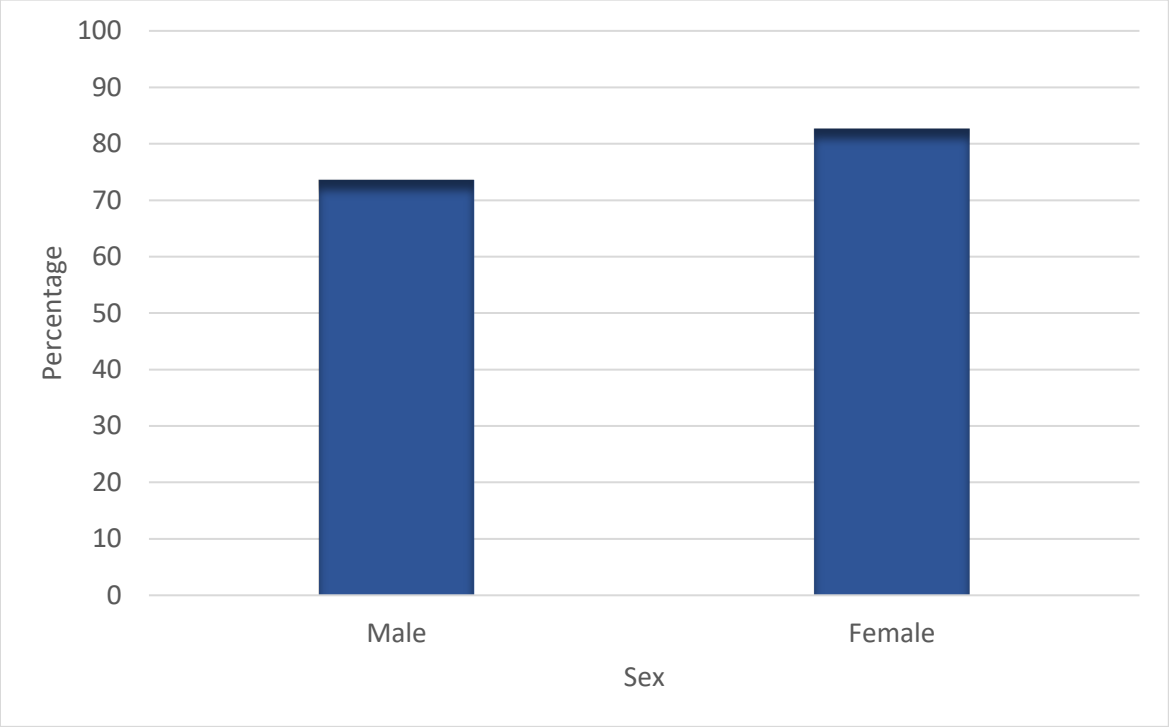
ADL: activities of daily living; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HR: heart rate; SBP: systolic blood pressure

Figure 20: Type of surgery by sex



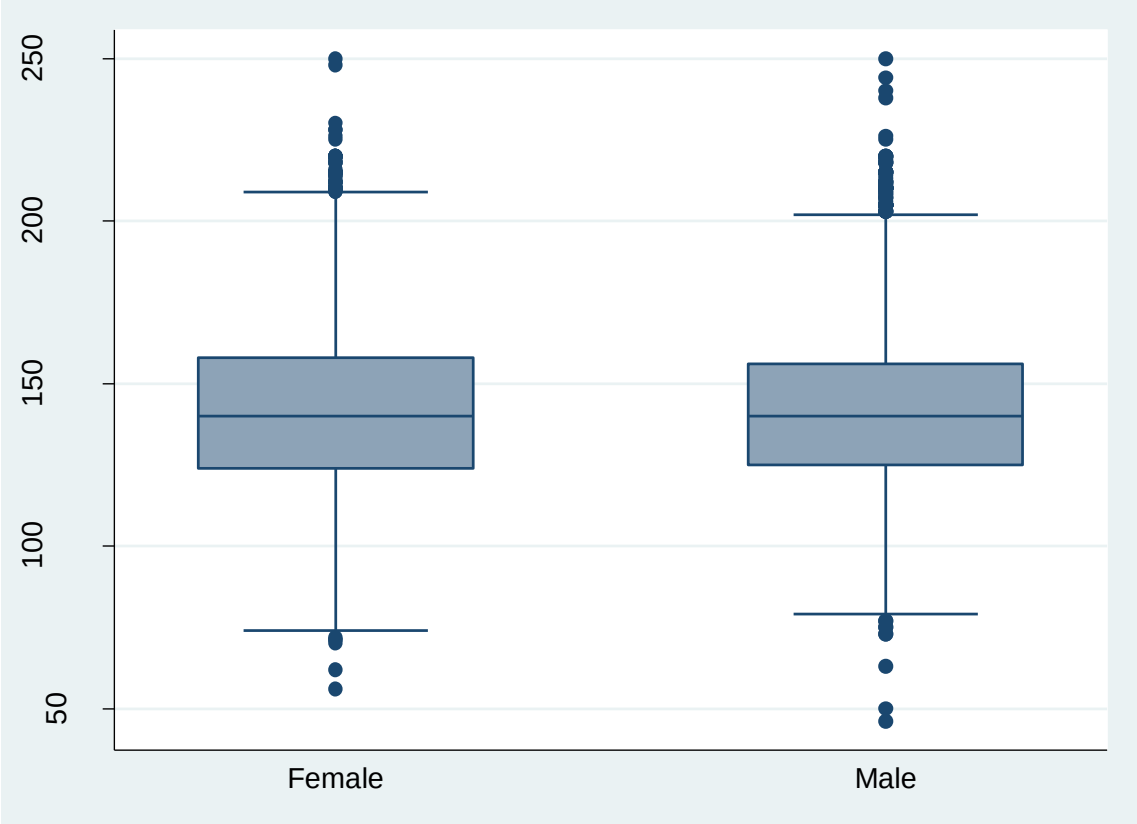
Bar graph illustrating the relationship between sex and high-risk surgeries. Y-axis: percentage of specific type of surgery. X-axis: sex.

Figure 21: Open surgery by sex



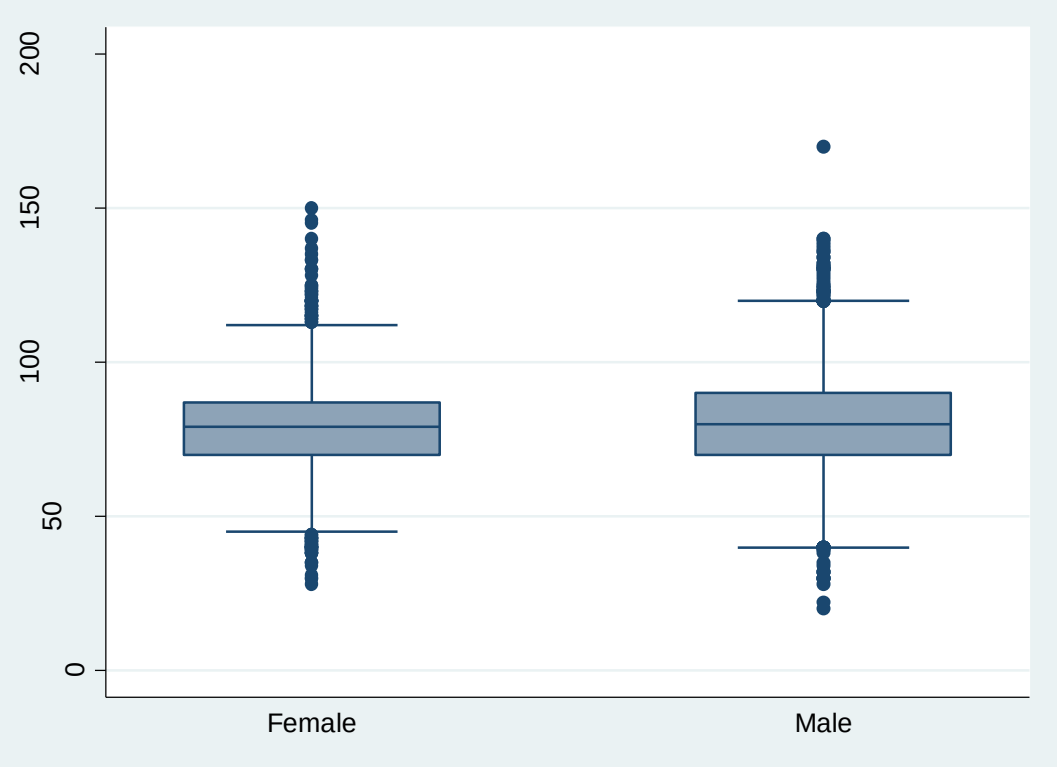
Bar graph illustrating the relationship between sex and open surgery. Y-axis: percentage of open surgery. X-axis: sex.

Figure 22: Preoperative SBP by sex



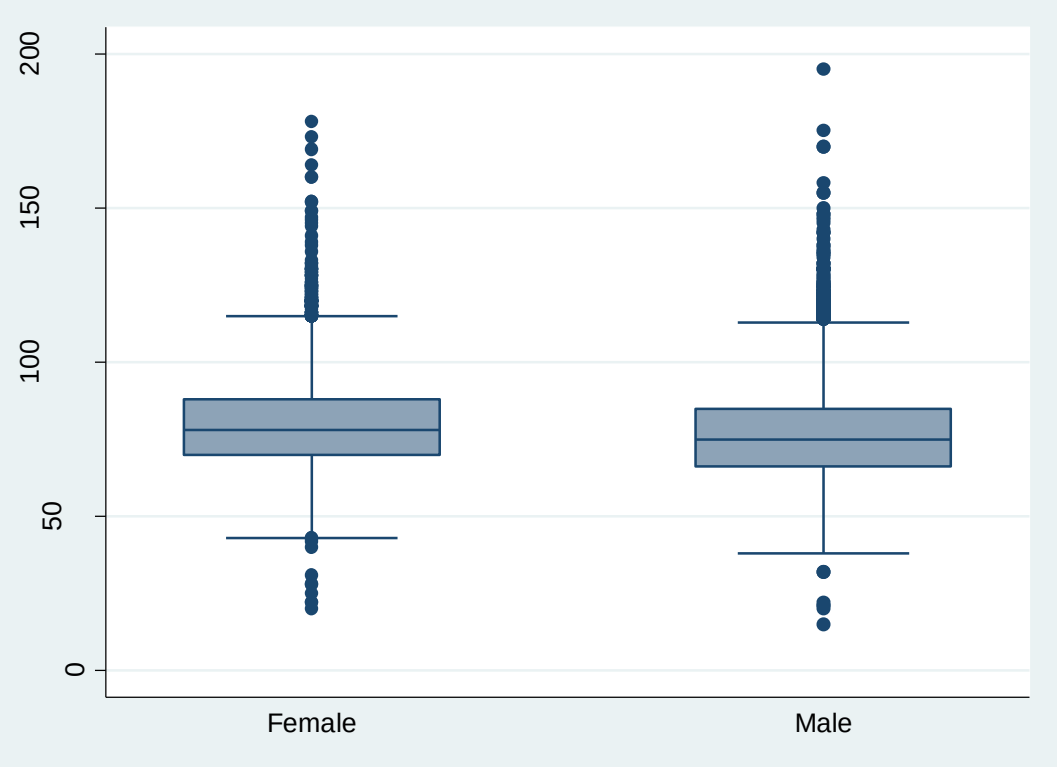
Box plot for preoperative systolic blood pressure by sex. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 23: Preoperative DBP by sex



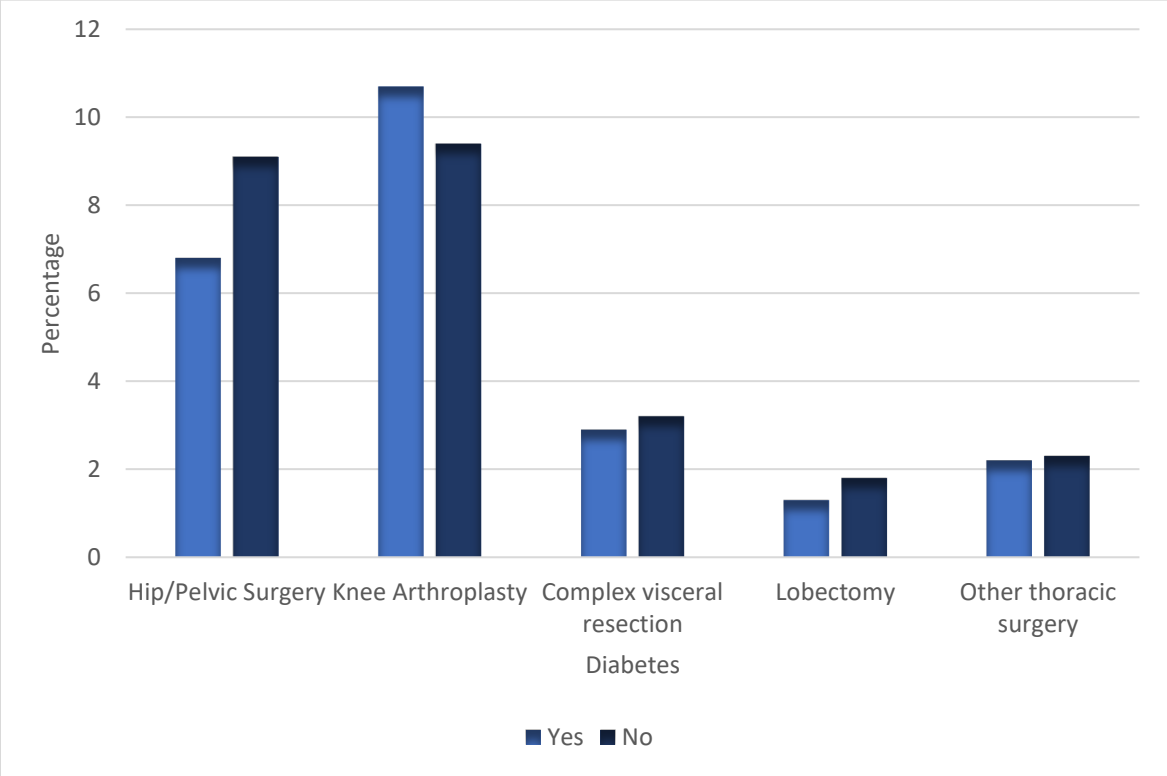
Box plot for preoperative diastolic blood pressure by sex. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 24: Preoperative heart rate by sex



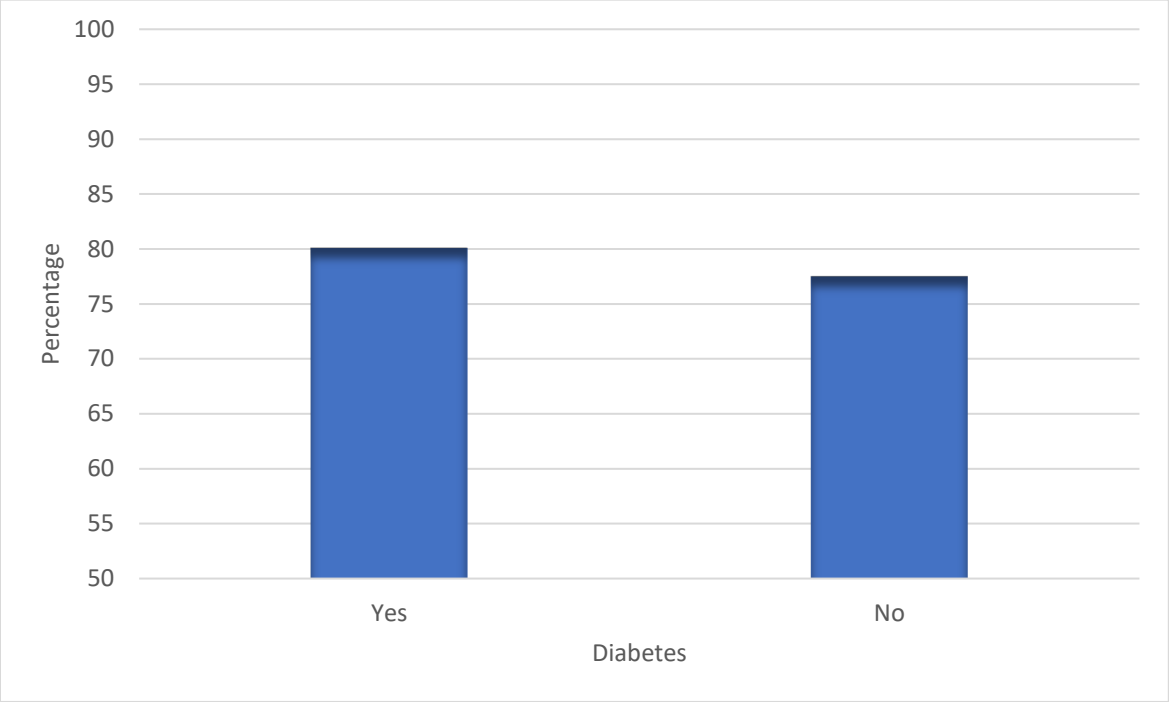
Box plot for preoperative heart rate by sex. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 25: Type of surgery by diabetic status



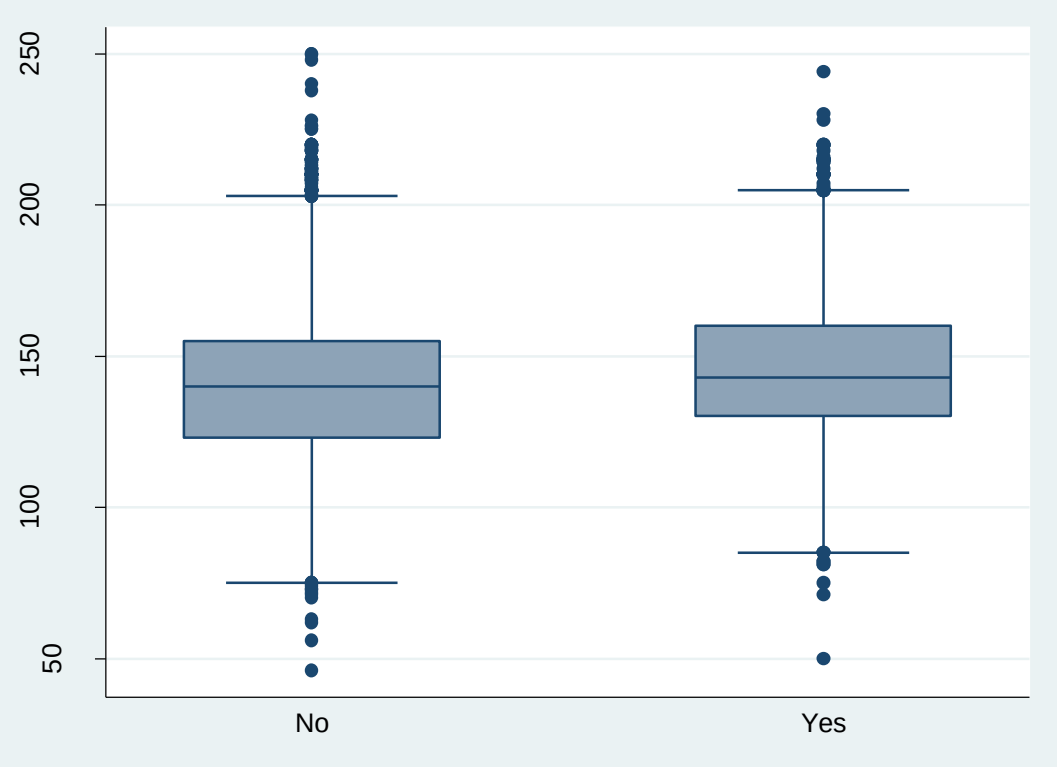
Bar graph illustrating the relationship between diabetic status and high-risk surgeries. Y-axis: percentage of specific type of surgery. X-axis: diabetic status.

Figure 26: Open surgery by diabetic status



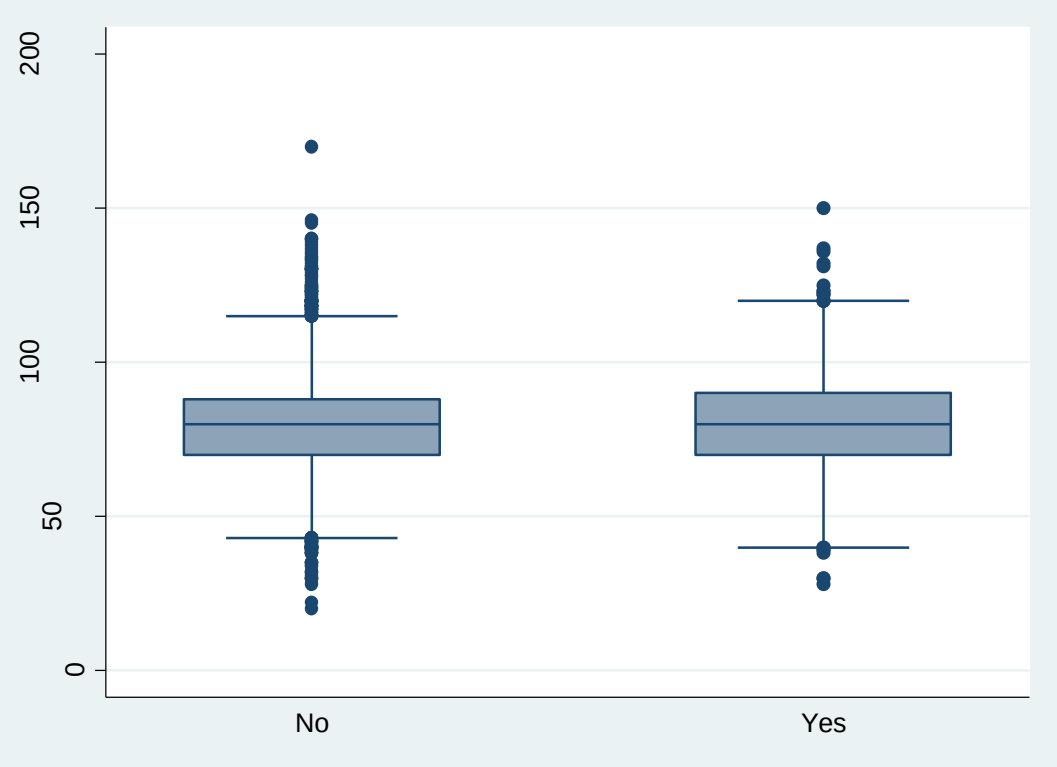
Bar graph illustrating the relationship between diabetic status and open surgery. Y-axis: percentage of open surgery. X-axis: diabetic status.

Figure 27: Preoperative SBP by diabetic status



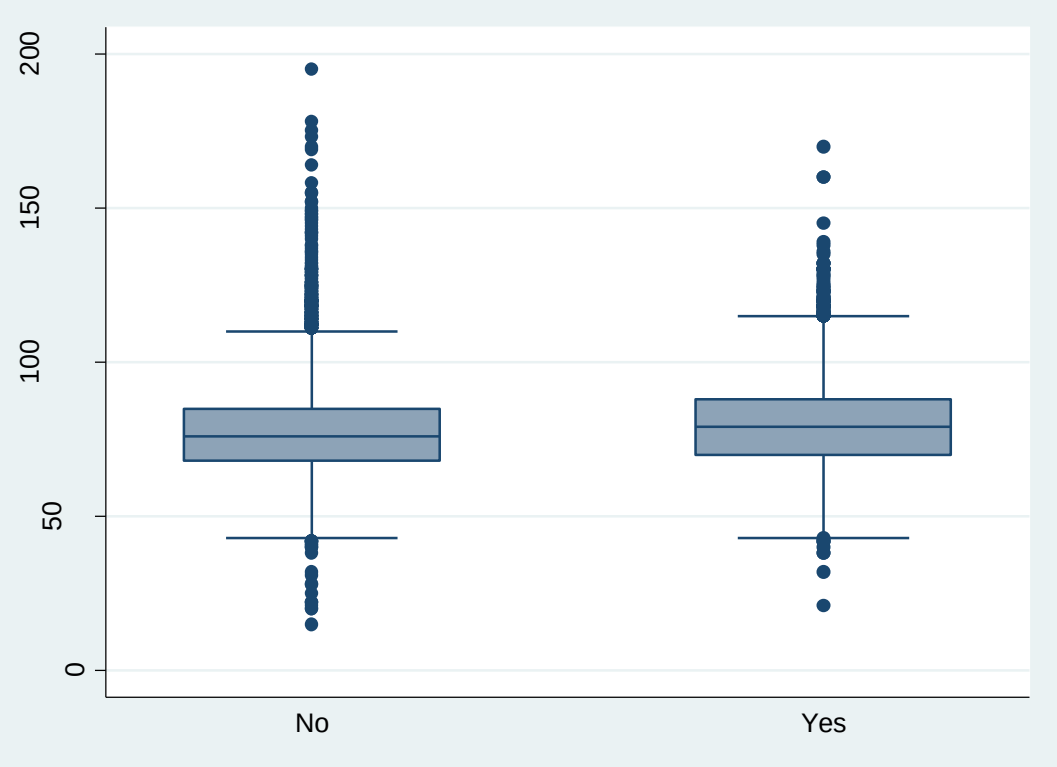
Box plot for preoperative systolic blood pressure by diabetic status. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 28: Preoperative DBP by diabetic status



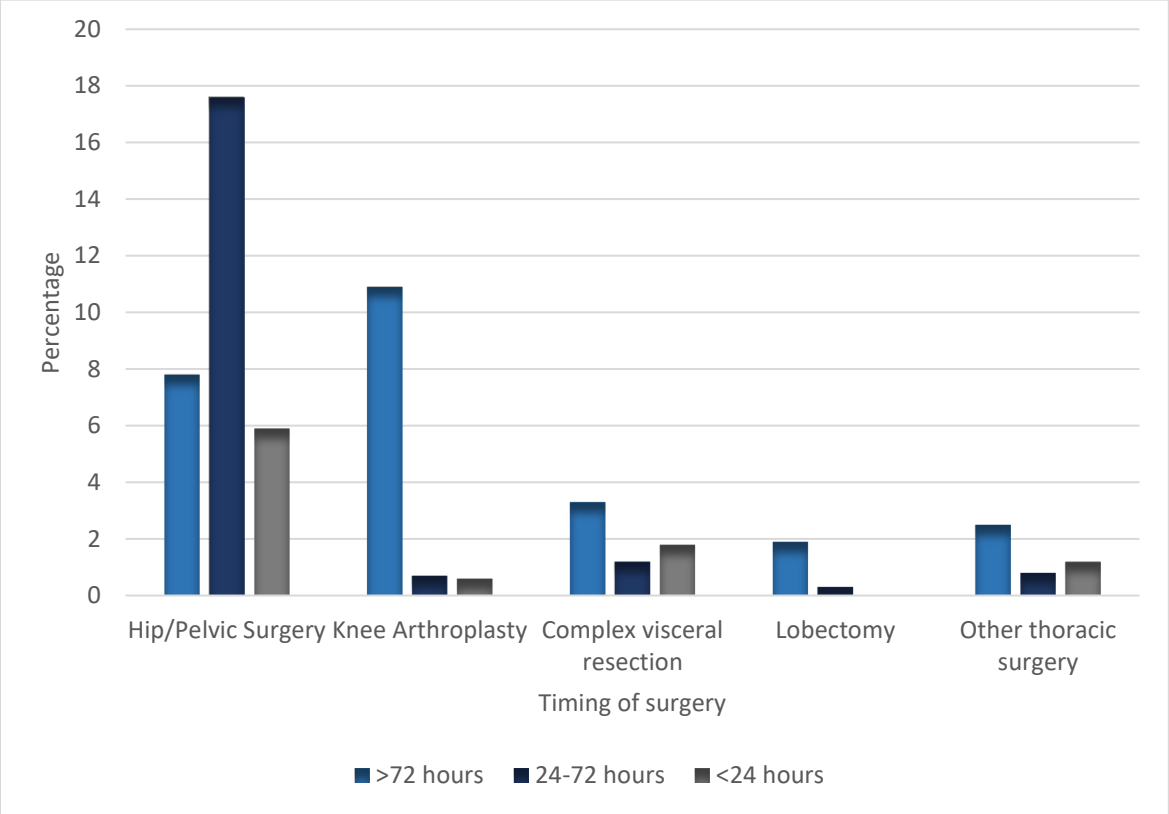
Box plot for preoperative diastolic blood pressure by diabetic status. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 29: Preoperative heart rate by diabetic status



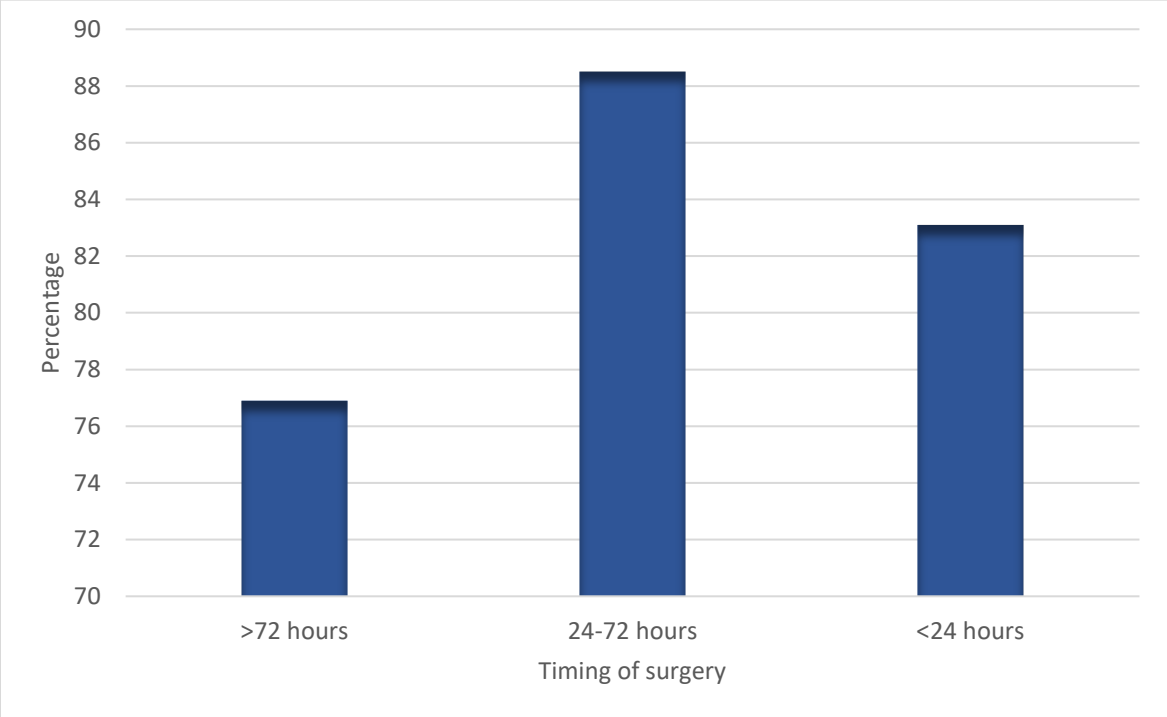
Box plot for preoperative heart rate by diabetic status. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 30: Type of surgery by timing



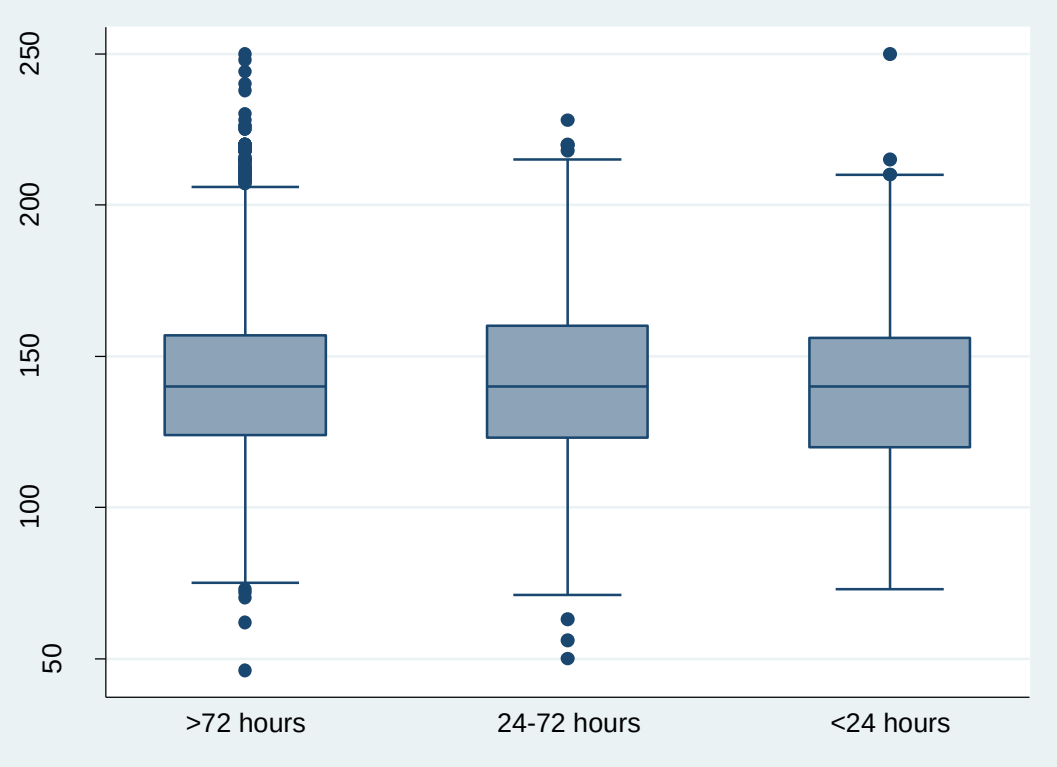
Bar graph illustrating the relationship between timing of surgery and high-risk surgeries. Y-axis: percentage of specific type of surgery. X-axis: timing of surgery.

Figure 31: Open surgery by timing



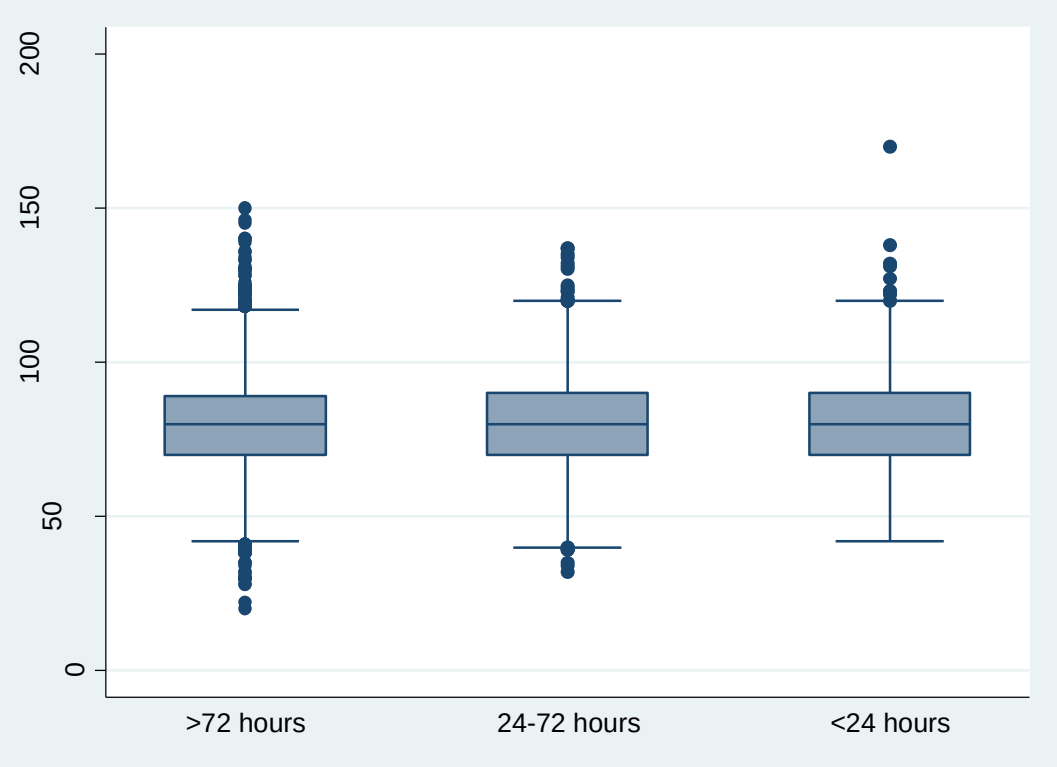
Bar graph illustrating the relationship between timing of surgery and open surgery. Y-axis: percentage of open surgery. X-axis: timing of surgery.

Figure 32: Preoperative SBP by timing



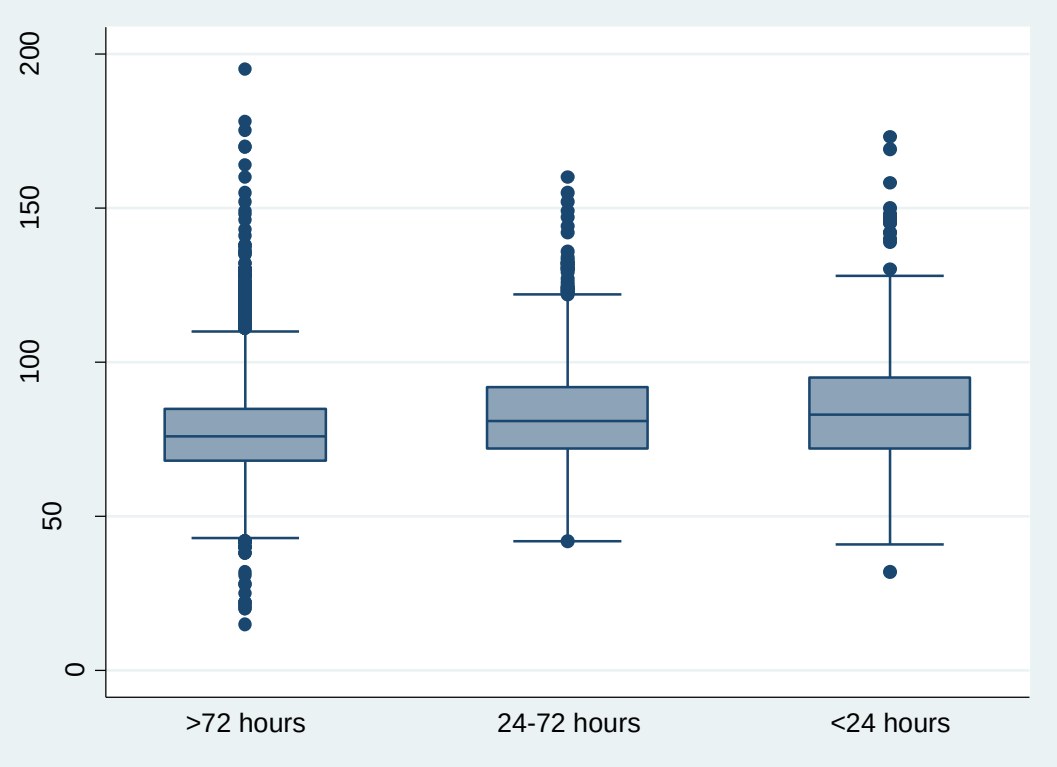
Box plot for preoperative systolic blood pressure by timing of surgery. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 33: Preoperative DBP by timing



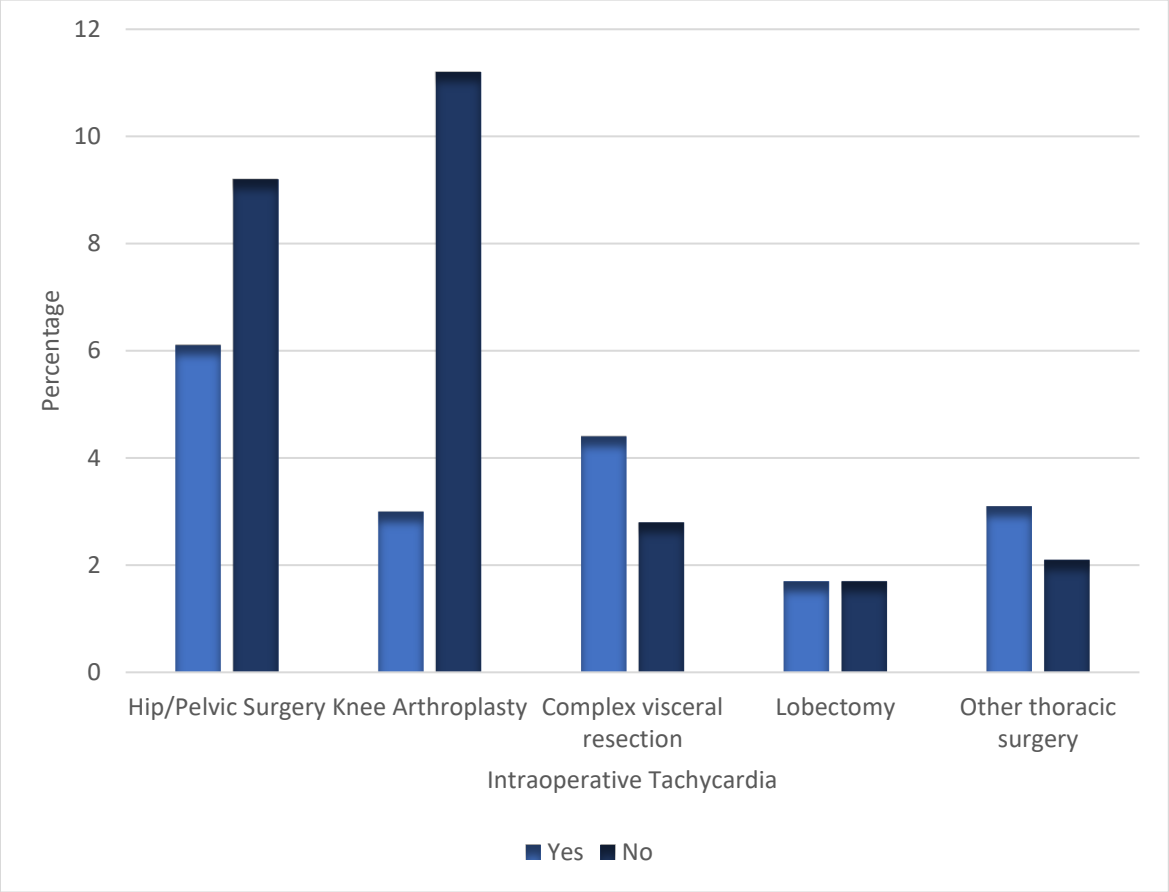
Box plot for preoperative diastolic blood pressure by timing of surgery. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 34: Preoperative heart rate by timing



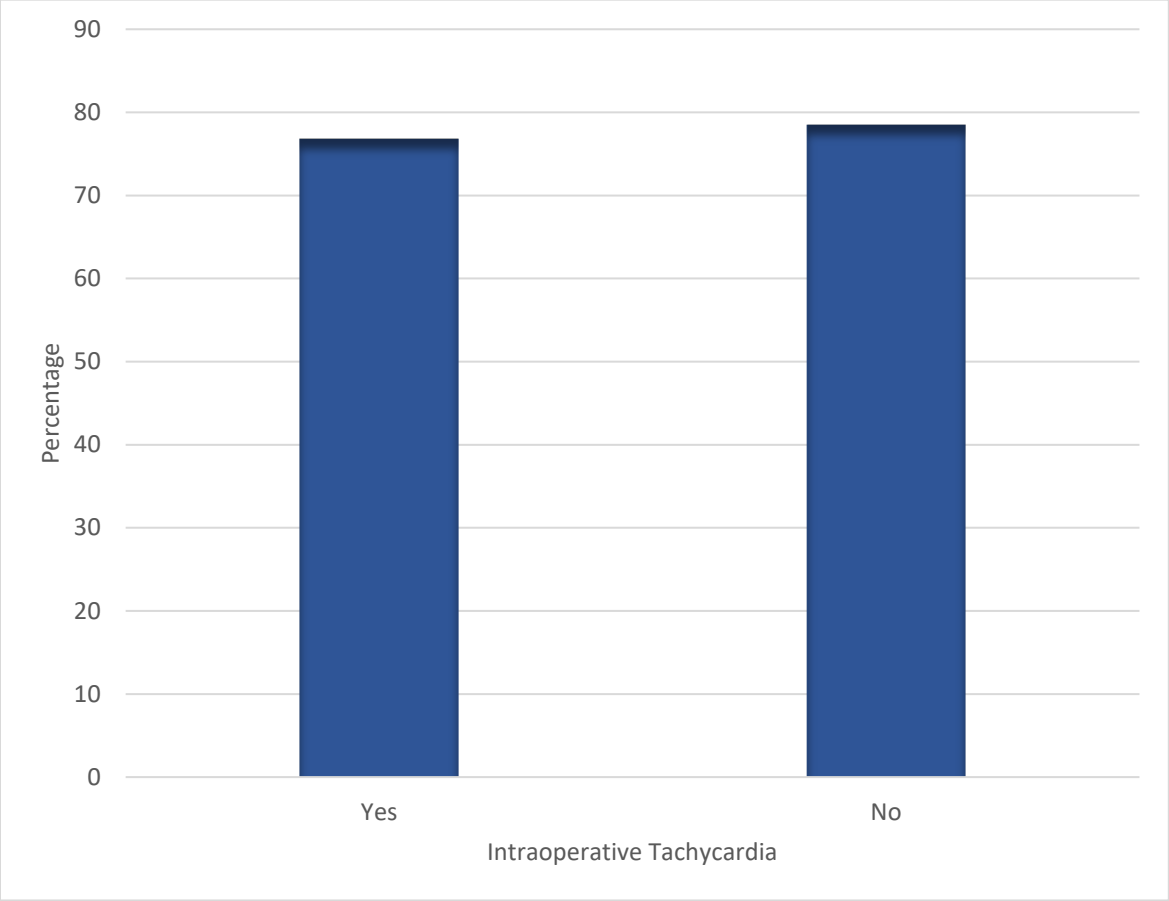
Box plot for preoperative heart rate by timing of surgery. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 35: Type of surgery by intraoperative tachycardia



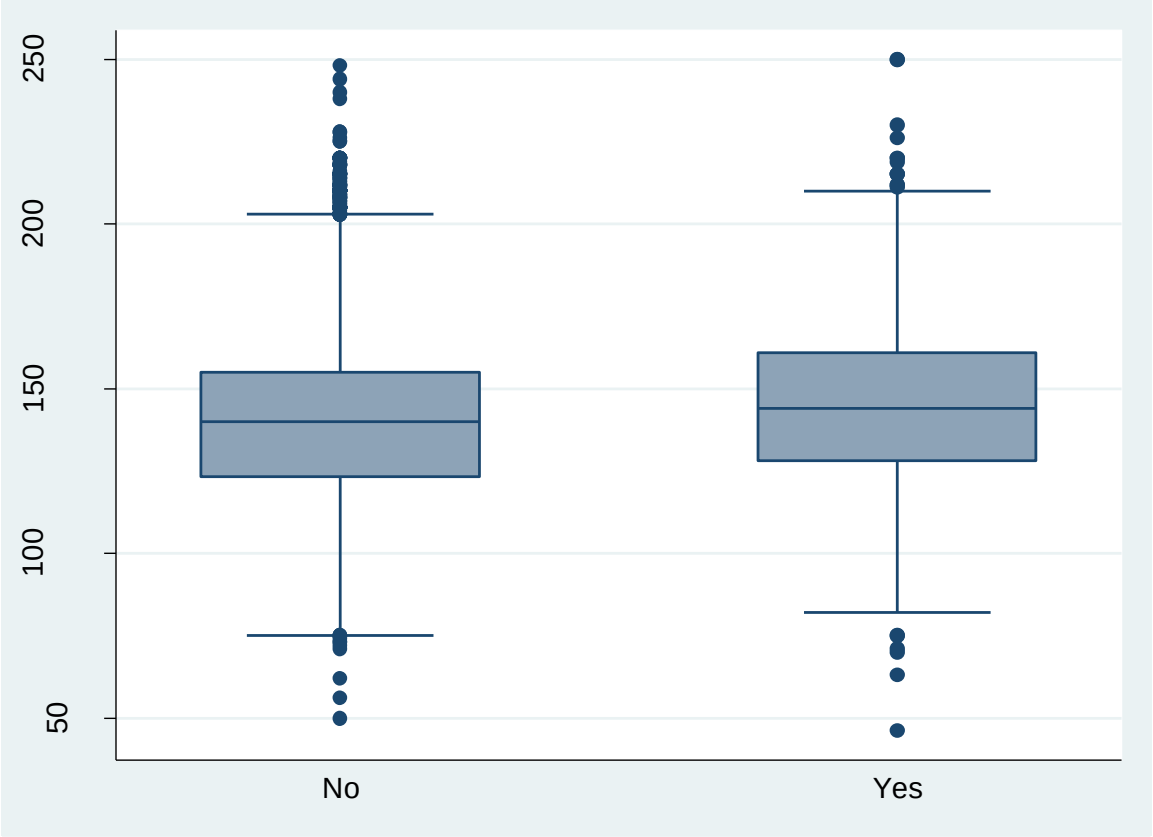
Bar graph illustrating the relationship between intraoperative tachycardia and high-risk surgeries. Y-axis: percentage of specific type of surgery. X-axis: intraoperative tachycardia.

Figure 36: Open surgery by intraoperative tachycardia



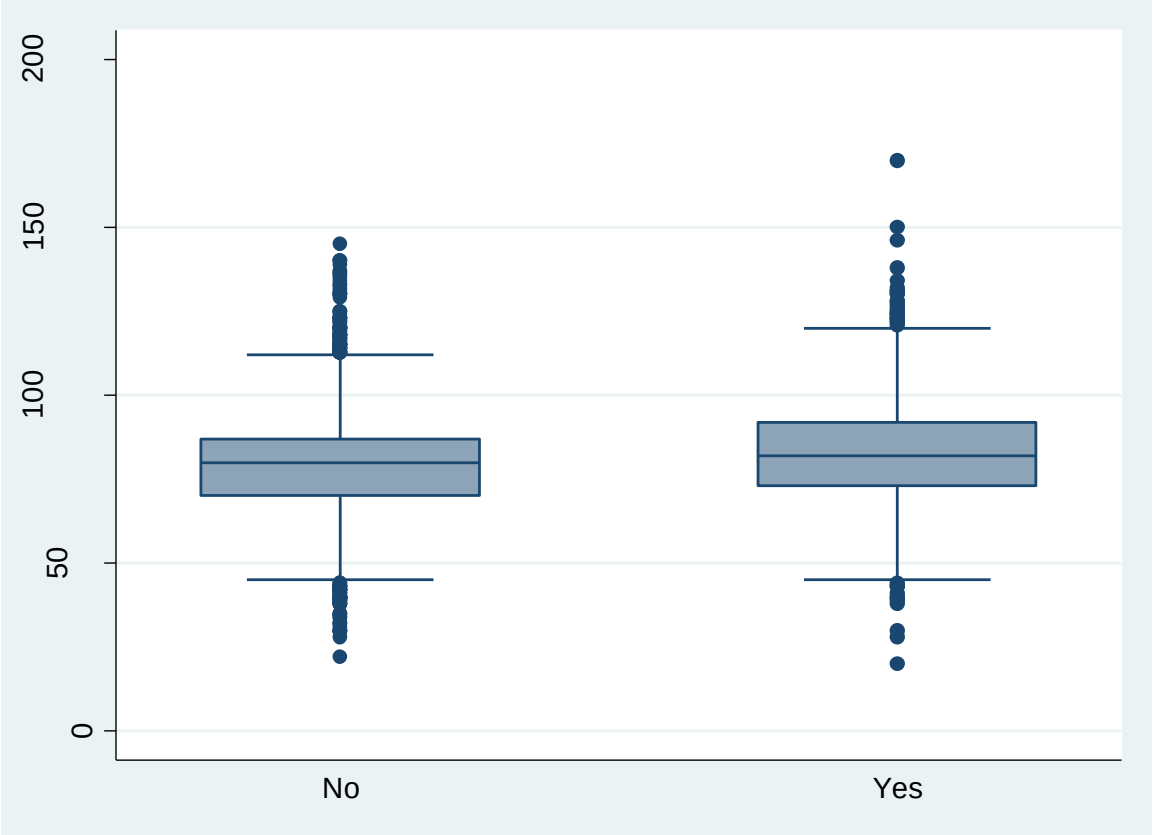
Bar graph illustrating the relationship between intraoperative tachycardia and open surgery. Y-axis: percentage of open surgery. X-axis: intraoperative tachycardia.

Figure 37: Preoperative SBP by intraoperative tachycardia



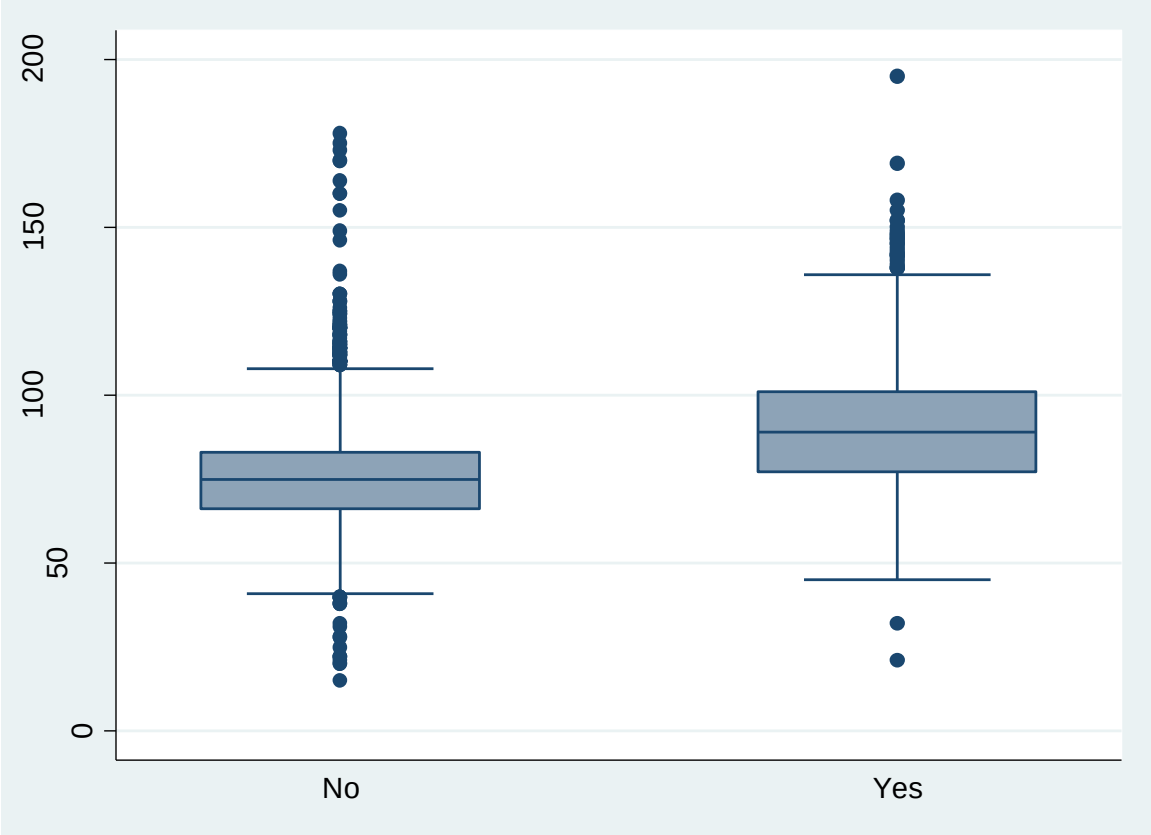
Box plot for preoperative systolic blood pressure by intraoperative tachycardia. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 38: Preoperative DBP by intraoperative tachycardia



Box plot for preoperative diastolic blood pressure by intraoperative tachycardia. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

Figure 39: Preoperative heart rate by intraoperative tachycardia



Box plot for preoperative heart rate by intraoperative tachycardia. Lower boundary of box: 25th percentile, line within the box: median, upper boundary of box: 75th percentile, whiskers above/below the box: 10th and 90th percentile, points above/below whiskers: outliers outside of the 10th percentiles.

6.2 Variable definitions

6.2.1 Surgical Variables

Major orthopaedic surgeries: A patient undergoing one or more of the following orthopedic surgeries: major hip or pelvis surgery, internal fixation of femur, knee arthroplasty, above knee amputations, or lower leg amputation (amputation below knee but above foot).

Major general surgeries: A patient undergoing one or more of the following general surgeries: complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, or major head and neck resection for non-thyroid tumor.

Major urology and gynaecology surgeries: A patient undergoing one or more of the following major urology or gynaecology surgeries: nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration, cytoreduction surgery, hysterectomy, radical prostatectomy, or transurethral prostatectomy.

Major neurosurgeries: A patient undergoing one or more of the following neurosurgeries: craniotomy or major spine surgery (i.e., surgery involving multiple levels of the spine).

Major vascular surgeries: A patient undergoing one or more of the following vascular surgeries: thoracic aorta reconstructive vascular surgery, aorto-iliac reconstructive vascular surgery, peripheral vascular reconstruction without aortic cross-clamping, extracranial cerebrovascular surgery, or endovascular abdominal aortic aneurysm repair.

Major thoracic surgeries: A patient undergoing one or more of the following thoracic surgeries: pneumonectomy, lobectomy, wedge resection of lung, resection of mediastinal tumor, or major chest wall resection.

Elective/Urgent/Emergency surgery: Emergency surgery was surgery that occurred <24 hours after a patient developed an acute surgical condition, urgent surgery was surgery that occurred 24-72 hours after a patient developed an acute surgical condition, elective surgery was surgery that occurred >72 hours after the patient developed a surgical condition.

Open/Endoscopic approach: Open surgery include both open surgeries and surgeries that started endoscopically and finished open, endoscopic surgery include all endoscopic, laparoscopic, thoracoscopic, endovascular, and arthroscopic approaches.

6.2.2 Patient characteristics

Age: The patient's age in years, calculated as the difference between their birthdate and the date of surgery and rounded down to the nearest year.

Preoperative hemoglobin: Latest available routinely measured preoperative hemoglobin value.

Preoperative estimated glomerular filtration rate (eGFR): Calculated using CKD-Epi equation and latest available routinely measured preoperative serum creatinine value.

Requires assistance with Activities of Daily Living: Patient requires assistance from another person with any of the following activities: dressing, eating, ambulating, toileting, hygiene**.** If a patient has suffered an acute injury leading to the need for surgery (e.g., hip fracture) the assessment for requirement of help for ADLs was based upon their condition prior to their acute injury.

Congestive heart failure: A physician diagnosis of a current or prior episode of congestive heart failure or prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema.

Recent high-risk coronary artery disease: Diagnosis ≤6 months prior to non-cardiac surgery of: a myocardial infarction, acute coronary syndrome, Canadian Cardiovascular Society Class (CCSC) III angina or CCSC IV angina.
CCSC III angina – angina occurring with level walking of 1-2 blocks or climbing ≤1 flight of stairs at a normal pace
CCSC IV – inability to perform any physical activity without the development of angina

Cerebral vascular event: A physician diagnosis of stroke, CT or MRI evidence of a prior stroke, or physician diagnosis of a prior transient ischemic attack (TIA).

Peripheral vascular disease: A current or prior history of: physician diagnosed intermittent claudication, vascular surgery for atherosclerotic disease, an ankle/arm systolic blood pressure ratio ≤ 0.90 in either leg at rest, or angiographic or doppler study demonstrating ≥ 70% stenosis in a non-cardiac artery.

Chronic Obstructive Pulmonary Disease (COPD): If the chart or a physician has ever indicated that a patient has chronic bronchitis, we accepted this as a patient having COPD. If there is no mention of this but the patient reported they have had daily production of sputum for at least 3 months in 2 consecutive years then they were marked as having COPD. Likewise, if a physician has ever indicated that a patient has emphysema or if a patient's Pulmonary Function Tests (PFT) state fixed or irreversible airflow limitation and/or emphysema then they were marked as having COPD.

Aortic stenosis: A physician diagnosis of aortic stenosis

Prior cardiac arrest: A patient with a prior history of a cardiac arrest.

Dialysis: defined as the use of a hemodialysis machine or peritoneal dialysis

Preoperative eGFR: Glomerular Filtration Rate estimated using the CKD-EPI equation using the most recent serum creatinine concentration measured before surgery.