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## Development and Validation of a Prediction Model for Stroke, Cardiac, and Mortality Risk After Non-Cardiac Surgery.

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ORIGINAL RESEARCH

# Development and Validation of a Prediction Model for Stroke, Cardiac, and Mortality Risk After Non-Cardiac Surgery

Sang H. Woo , MD; Gregory D. Marhefka , MD; Scott W. Cowan , MD; Lily Ackermann , MD, ScM

**BACKGROUND:** Commonly used cardiovascular risk calculators do not provide risk estimation of stroke, a major postoperative complication with high morbidity and mortality. We developed and validated an accurate cardiovascular risk prediction tool for stroke, major cardiac complications (myocardial infarction or cardiac arrest), and mortality after non-cardiac surgery.

**METHODS AND RESULTS:** This retrospective cohort study included 1 165 750 surgical patients over a 4-year period (2007–2010) from the American College of Surgeons National Surgical Quality Improvement Program Database. A predictive model was developed with the following preoperative conditions: age, history of coronary artery disease, history of stroke, emergency surgery, preoperative serum sodium ( $\leq 130$  mEq/L,  $>146$  mEq/L), creatinine  $>1.8$  mg/dL, hematocrit  $\leq 27\%$ , American Society of Anesthesiologists physical status class, and type of surgery. The model was trained using American College of Surgeons National Surgical Quality Improvement Program data from 2007 to 2009 ( $n=809\ 880$ ) and tested using data from 2010 ( $n=355\ 870$ ). Risk models were developed using multivariate logistic regression. The outcomes were postoperative 30-day stroke, major cardiovascular events (myocardial infarction, cardiac arrest, or stroke), and 30-day mortality. Major cardiac complications occurred in 0.66% ( $n=5332$ ) of patients (myocardial infarction, 0.28%; cardiac arrest, 0.41%), postoperative stroke in 0.25% ( $n=2005$ ); 30-day mortality was 1.66% ( $n=13\ 484$ ). The risk prediction model had high predictive accuracy with area under the receiver operating characteristic curve for stroke (training cohort=0.869, validation cohort=0.876), major cardiovascular events (training cohort=0.871, validation cohort=0.868), and 30-day mortality (training cohort=0.922, validation cohort=0.925). Surgery types, history of stroke, and coronary artery disease are significant risk factors for stroke and major cardiac complications.

**CONCLUSIONS:** Postoperative stroke, major cardiac complications, and 30-day mortality can be predicted with high accuracy using this web-based predictive model.

**Key Words:** myocardial infarction ■ prediction ■ stroke ■ surgery

Stroke is a rare, life threatening complication of surgery with high morbidity and mortality.<sup>1</sup> Mortality from postoperative stroke was reported to be 26% after general surgery procedures and can increase to 60% in those with prior stroke.<sup>2,3</sup> Furthermore, patients experiencing in-hospital stroke have worse outcomes compared with community-onset stroke, where nearly 50% of the in-patient strokes in 1 cohort were perioperative.<sup>4</sup> Because stroke in the postoperative period

is associated with a delay to diagnostic imaging and lower use of thrombolysis given the risks of recent surgery, surgical patients are at higher risk for poor outcomes.<sup>4</sup>

Accurate assessment of postoperative risk using readily available clinical information helps determine the need for change in management in the perioperative period and timing of surgery. Consequently, the American Heart Association and American College of

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## CLINICAL PERSPECTIVE

### What Is New?

- A non-cardiac surgery risk prediction tool newly includes 30-day postoperative stroke risk, along with major cardiac complications and mortality.
- This new risk model was developed based on >1 million patients from the American College of Surgeons National Surgical Quality Improvement Program Database.
- The risk model includes 9 predictors and has excellent predictive performance.

### What Are the Clinical Implications?

- The important clinical risk of postoperative stroke can now be stratified along with standard cardiac complications and mortality risk using this web-based risk model during preoperative evaluation.
- Individualized risk assessment of stroke, cardiac complications, and mortality helps clinicians better counsel patients and inform surgeons and possibly implement measures to lower the risk.

## Nonstandard Abbreviations and Acronyms

<b>ACS-NSQIP</b>	American College of Surgeons National Surgical Quality Improvement Program Database
<b>EVAR</b>	endovascular aneurysm repair

Cardiology guidelines emphasize the use of clinical risk factors for preoperative cardiac evaluation.<sup>5</sup>

A major drawback of commonly used risk estimators is a lack of assessment for postoperative stroke risk. The Revised Cardiac Risk Index and Gupta Myocardial Infarction or Cardiac Arrest (MICA) risk calculator have been used extensively to predict postoperative cardiac complications.<sup>6</sup> Revised Cardiac Risk Index is limited by relatively moderate predictive accuracy (area under the curve [AUC], 0.759).<sup>7,8</sup> The Gupta MICA risk calculator is only limited to myocardial infarction or cardiac arrest.<sup>6</sup> These calculators do not estimate the risk of stroke, and mortality. The Universal American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Surgical Risk Calculator includes 21 preoperative factors to predict 8 outcomes.<sup>9</sup> This calculator also does not assess the risk of postoperative stroke and its inclusion of 21 predictors limits its ease of use and utility by clinicians.

The aim of this study is to identify risk factors for stroke, major cardiovascular complications, and 30-day mortality.

## METHODS

### Study Participants

All data in this study are available from the ACS-NSQIP. Data used in the analysis were extracted from the ACS-NSQIP database from 2007 to 2010. The ACS-NSQIP data set is a multicenter, prospective database with >500 US and international hospitals (academic, community) participating in data collection.<sup>10,11</sup> Trained surgical clinical reviewers at each participating hospital compiled the data. Each patient was followed for 30 days after surgery and complications within this period were included in the database.<sup>12</sup> Variables examined in the analysis included age, sex, smoking, alcohol use (>2 drinks/day in 2 weeks before admission), history of coronary artery disease (defined as myocardial infarction within 6 months of surgery, history of angina within 1 month before surgery, previous percutaneous coronary intervention), previous cardiac surgery, history of congestive heart failure, history of stroke, hypertension medication use, peripheral vascular disease, chronic obstructive pulmonary disease, dyspnea, weight loss, bleeding disorder, dialysis, steroid use, rest pain, preoperative sepsis, chemotherapy, disseminated cancer, esophageal varices, ascites, emergency procedure, diabetes mellitus, acute renal failure (defined by increase in blood urea nitrogen and a rising creatinine of >3 mg/dL, within 24 hours before surgery), hemiplegia, quadriplegia, paraplegia, American Society of Anesthesiologists physical status class, and preoperative functional status. Risk factors are further described in Table 1. Preoperative laboratory testing included in the analysis were serum sodium, creatinine, white blood cell, platelet, and hematocrit. Vascular surgery was divided into carotid endarterectomy, endovascular aneurysm repair (EVAR), thoracic EVAR, suprainguinal bypass, infrainguinal bypass, open aortic aneurysm repair, other vascular surgery as described previously.<sup>13,14</sup> Figure S1 shows the study participant flowchart.

### Outcome

The outcomes were 30-day postoperative stroke, major cardiovascular events (myocardial infarction, cardiac arrest, or stroke), or 30-day postoperative mortality.

Stroke is defined by the ACS-NSQIP as "An embolic, thrombotic, or hemorrhagic vascular accident or stroke with motor, sensory, or cognitive dysfunction (eg, hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) that persists for 24 or more hours".<sup>15</sup>

**Table 1. Characteristics of the Patients (Patients From 2007–2009)**

	No MI/ Arrest (n=804 548)	MI/Arrest (n=5332)	Unadjusted Odds Ratio (95% CI) for MI/ Arrest	No Stroke (n=807 875)	Stroke (n=2005)	Unadjusted Odds Ratio (95% CI) For Stroke
Age, y (mean±SD)	55.4 (±17.1)	69.8 (±13.0)	1.059 (1.057–1.061)	55.4 (±17.2)	70.0 (±13.6)	1.06 (1.056–1.063)
Sex (men) (%)	42.52	57.58	1.83 (1.74–1.94)	42.6	48.8	1.29 (1.18–1.4)
ASA class* 1 (%) (Ref=1)	9.90	0.24		9.86	0.40	
2	46.00	7.71	6.82 (3.93–11.85)	45.83	10.9	5.89 (2.91–11.93)
3	37.62	48.9	52.83 (30.63–91.11)	37.65	56.26	36.94 (18.43–74.04)
4	6.20	38.14	248.78 (144.19–429.24)	6.35	30.22	117.58 (58.53–236.21)
5	0.27	5.09	767.5 (439.25–1341.04)	0.30	2.19	182.6 (85.87–388.26)
Diabetes mellitus (%)	14.79	32.15	2.73 (2.58–2.89)	14.9	26.78	2.09 (1.9–2.31)
Alcohol use >2 drinks/day in 2 wks before admission (%)	2.61	3.98	1.54 (1.34–1.77)	2.6	4.84	1.89 (1.54–2.32)
Chemotherapy (%)	1.06	1.82	1.73 (1.42–2.12)	1.06	1.35	1.27 (0.87–1.86)
Disseminated cancer (%)	1.93	4.24	2.25 (1.97–2.57)	1.94	2.74	1.42 (1.09–1.86)
Paraplegia (%)	0.49	0.99	2.04 (1.56–2.68)	0.49	0.75	1.53 (0.92–2.54)
Quadriplegia (%)	0.13	0.43	3.38 (2.24–5.12)	0.13	0.15	1.15 (0.37–3.58)
Hemiplegia (%)	0.92	2.87	3.17 (2.70–3.73)	0.92	6.93	8.01 (6.74–9.54)
Smoker within 1 y (%)	20.68	24.46	1.24 (1.17–1.32)	20.69	26.43	1.38 (1.25–1.52)
Pack-year of smoking	10.59	23.73	1.02 (1.01–1.02)	10.64	23.44	1.01 (1.01–1.02)
Esophageal varices (%)	0.12	0.32	2.72 (1.68–4.4)	0.12	0.05	0.42 (0.06–2.98)
Chronic obstructive pulmonary disease (%)	4.73	16.97	4.12 (3.83–4.42)	4.79	14.11	3.27 (2.88–3.71)
Ascites (%)	1.01	5.29	5.46 (4.83–6.17)	1.04	2.19	2.14 (1.59–2.89)
Congestive heart failure (%)	0.83	7.28	9.41 (8.46–10.46)	0.86	4.49	5.41 (4.38–6.7)
Myocardial infarction (%)	0.58	5.61	10.2 (9.04–11.5)	0.60	3.84	6.57 (5.22–8.26)
Previous cardiac surgery (%)	5.73	21.23	4.43 (4.15–4.74)	5.80	18.45	3.67 (3.28–4.11)
Previous percutaneous coronary intervention (%)	5.33	17.74	3.83 (3.57–4.11)	5.40	12.77	2.56 (2.25–2.93)
Angina (%)	0.68	4.05	6.12 (5.33–7.04)	0.70	2.84	4.14 (3.18–5.4)
Peripheral vascular disease (%)	4.00	17.18	4.98 (4.63–5.35)	4.06	13.17	3.58 (3.14–4.08)
Hypertension on medication (%)	45.65	77.83	4.18 (3.92–4.46)	45.8	77.61	4.1 (3.69–4.56)
Acute renal failure (%)	0.55	5.98	11.47 (10.2–12.89)	0.58	3.14	5.55 (4.31–7.14)
Dialysis (%)	1.97	12.23	6.93 (6.38–7.54)	2.03	5.79	2.97 (2.46–3.58)
Steroid (%)	3.05	7.48	2.57 (2.32–2.85)	3.08	5.99	2.01 (1.67–2.41)
Stroke with neurologic deficit (%)	2.30	7.95	3.67 (3.32–4.05)	2.31	15.91	8.02 (7.11–9.04)
Stroke with no neurologic deficit (%)	2.01	6.06	3.14 (2.81–3.52)	2.02	9.93	5.35 (4.62–6.2)
Transient ischemic attack (%)	2.89	7.69	2.8 (2.53–3.09)	2.89	15.31	6.07 (5.37–6.86)
Weight loss (%)	2.23	6.98	3.29 (2.96–3.66)	2.26	4.19	1.89 (1.52–2.36)
Bleeding disorder (%)	5.52	20.46	4.4 (4.11–4.71)	5.58	20.75	4.43 (3.97–4.93)
Emergency (%)	12.39	34.02	3.65 (3.44–3.86)	12.50	26.63	2.54 (2.3–2.81)
Rest Pain (%)	2.28	11.07	5.33 (4.89–5.82)	2.32	8.13	3.72 (3.17–4.37)
White blood count, (10 <sup>9</sup> /L)	8.44	10.69		8.45	9.72	
Hematocrit (%)	38.98	35.02		38.95	36.61	
Platelet (10 <sup>9</sup> /L)	261.5	240.72		261.4	246.67	
Partial thromboplastin time	30.79	34.61		30.82	33.91	
International normalized ratio	1.11	1.28		1.11	1.19	

\*ASA class indicates American Society of Anesthesiologists Physical Status Classification; and MI, myocardial infarction.

Cardiac arrest is defined by the ACS-NSQIP as “The absence of cardiac rhythm or presence of chaotic cardiac rhythm which results in a cardiac arrest

requiring the initiation of CPR. Patients are included who are in a pulseless ventricular tachycardia or ventricular fibrillation in which defibrillation is performed

and pulseless electrical activity arrest requiring chest compressions.”<sup>15</sup> Myocardial infarction was defined in the ACS-NSQIP database as “A new transmural acute myocardial infarction occurring during surgery or within 30 days as manifested by new Q-waves on ECG.”<sup>15</sup>

## Statistical Analysis

A risk prediction model was built based on the data set from 2007 to 2009 (n=809 880). The data set from 2010 (n=355 870) was used to test and validate the predictive model. Patient risk factors were compared using  $\chi^2$  for categorical variables and Wilcoxon for continuous variables. Bivariate odds ratio with 95% CI were calculated.

Clinical predictors were selected using backwards elimination using Akaike information criterion for cardiac complications, stroke complications, and mortality. Predictors that were significant in cardiac, stroke, and mortality were included in the model. Even though coronary artery disease history was not selected based on the Akaike information criterion for stroke model, it was included in the final model because of its clinical importance in cardiac risk prediction.

The logistic regression models were constructed with 30-day postoperative cardiac complications, stroke complications, and death as the dependent variables. Multivariate logistic regression analysis was performed for predictor coefficient and adjusted odds ratio. AUC was used for model evaluation. Best model parameters were selected using GridSearchCV package with 5-fold cross validation. Missing laboratory values (hematocrit, creatinine, and sodium) had separate categorical levels.

Statistical analysis was performed with Python (version 3.6.6.), Statsmodels (version 0.9.0), r programming (RStudio version 1.1.463). Scikit-learn was used for machine learning modeling.<sup>16</sup> This study was approved by Thomas Jefferson University institutional review board, and informed consent from study participants was waived.

## RESULTS

### Study Population

A total of 1 165 750 patients from 2007 to 2010 were included in the analysis and 57.4% were women. A risk prediction model was developed based on 809 880 participants from 2007 to 2009. Table 1 shows characteristics of study participants from the years 2007 to 2009. Major cardiac complications were prevalent in 0.66% (n=5332) of patients (myocardial infarction, 0.28%; cardiac arrest, 0.41%). Postoperative stroke was found in 0.25% (n=2005) of patients. The stroke

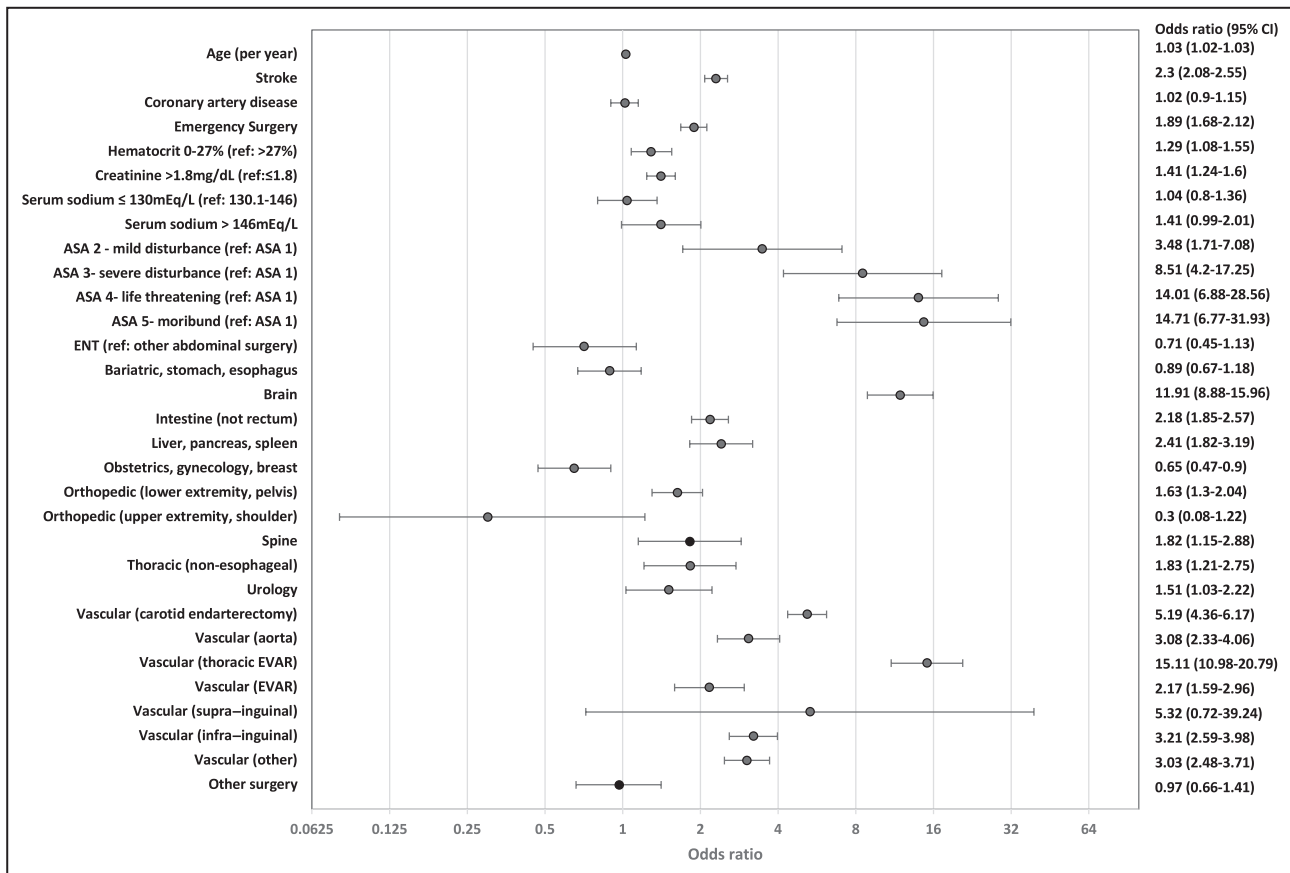
rate was similar to prior studies reporting an incidence of strokes between 0.1% and 0.7% in patients undergoing non-cardiac surgery;<sup>17–20</sup> 1.66% (n=13 484) of patients died within 30 days after surgery. Patients with postoperative cardiac complications and stroke were significantly older than patients who did not have these complications ( $P<0.001$ ). History of stroke and transient ischemic attack are also significantly associated with a high rate of postoperative stroke (odds ratio [OR]=8.02, 6.07;  $P<0.001$ ). Patients with major cardiac complications had higher prevalence of preoperative coronary artery disease. A history of percutaneous coronary intervention, prior cardiac surgery, and prior myocardial infarction were likewise significantly associated with major cardiac events (OR=3.83, 4.43, 10.2;  $P<0.001$ ). Preoperative renal dysfunction including acute renal failure was significantly associated with postoperative major cardiac complications (OR=11.47;  $P<0.001$ ) and stroke (OR=5.55;  $P<0.001$ ) with dialysis as a strong predictor of cardiovascular morbidity (cardiac events OR=6.93; stroke OR=2.97;  $P<0.001$ ).

### Stroke, Myocardial Infarction, and Mortality Rate

Patients with a postoperative stroke had a high 30-day unadjusted mortality rate (23.8%), at a rate similar to prior studies.<sup>2,17,19</sup> Postoperative stroke had an OR of 19.08 (95% CI, 17.19–21.17) for death within 30 days postoperatively. The unadjusted mortality rate associated with stroke is similar to that for postoperative myocardial infarction (24.4%, OR=19.88; 95% CI, 18.05–21.90). Our study showed 15.8% of myocardial infarctions, 10.9% of cardiac arrests, and 25.0% of strokes occurred after the initial hospital stay.

### Prediction of Postoperative Stroke

Figure 1 and Table S1 show predictors of postoperative stroke in a multivariate model. History of stroke, including transient ischemic attack, is significantly associated with postoperative stroke complications ( $P<0.001$ ; OR=2.3). Emergency surgery is also highly significant ( $P<0.001$ ; OR=1.89). Three other predictors (age, preoperative serum hematocrit, creatinine) were also found to be significant. Figure S2 shows unadjusted stroke complication rates according to preoperative serum sodium, creatinine, and hematocrit levels. Anemia (hematocrit  $\leq 27\%$ ) is associated with increased risk of stroke (OR=1.29;  $P<0.001$ ). The risk of stroke also increases with renal dysfunction (serum creatinine  $>1.8$  mg/dL; OR=1.41;  $P<0.001$ ). Specific types of high-risk surgery such as carotid endarterectomy, thoracic EVAR, vascular-aorta surgery, and brain surgery are significantly associated with stroke.



**Figure 1. Forest plot and adjusted odds ratio of predictors for 30-day postoperative stroke complication.** ASA indicates American Society of Anesthesiologists Physical Status Classification; ENT-ear, nose, throat; and EVAR-endovascular aneurysm repair.

However, there is no significant association with history of coronary artery disease ( $P=0.73$ ). The model has excellent AUC (training cohort=0.869, validation cohort=0.876) and brier score (0.002). Figure S3A shows excellent calibration.

### Prediction of Postoperative Major Cardiac and Cerebrovascular Complications – Myocardial Infarction, Cardiac Arrest, and/or Stroke

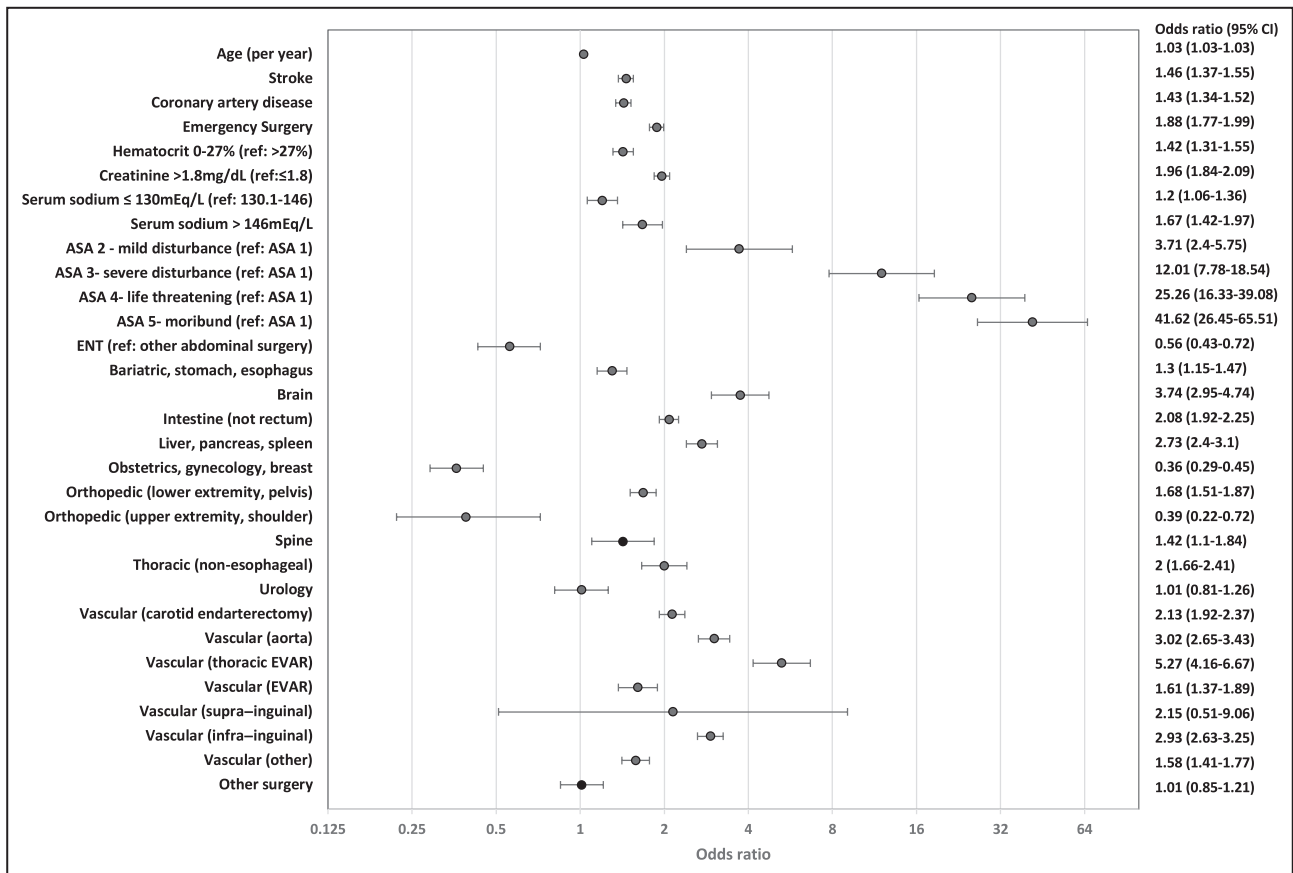
Figure 2 and Table S2 show predictors of major cardiovascular complications in a multivariate model. The major complications include the occurrence of myocardial infarction, cardiac arrest, or stroke within 30 days after surgery. History of coronary artery disease and stroke were significant predictors with high adjusted odds of major complications (adjusted OR=1.43, 1.46). Hypernatremia (serum sodium >146 mEq/L) was associated with increased risk of major complications (OR=1.67;  $P<0.001$ ). Hyponatremia (serum sodium ≤130 mEq/L) also had increased risk (OR=1.2;  $P<0.001$ ). Compared with reference renal function (serum creatinine, Cr [0–1.8 mg/dL]), renal dysfunction

(>1.8 mg/dL) has increased adjusted odds of complications (OR=1.96;  $P<0.001$ ). Anemia was another predictor that had high adjusted odds of major complications. Serum hematocrit (≤27%) has increased odds (1.42 [95% CI, 1.31–1.55]). Figure S4 shows unadjusted major cardiovascular complication rates according to serum sodium, creatinine, and hematocrit from the patient cohort in 2007 to 2009. The model for major cardiovascular complications had excellent AUC (training cohort=0.871, validation cohort=0.868) and brier score (0.008). Figure S3B shows excellent calibration.

In predicting postoperative 30-day myocardial infarction, stroke and death, this model has greater predictive power in the validation cohort (AUC, 0.904) compared with the Dakik cardiovascular index (AUC, 0.82).<sup>21</sup>

### Prediction of Postoperative Myocardial Infarction and Cardiac Arrest

The cardiac risk model with 9 predictors has excellent AUC (training cohort=0.879, validation cohort=0.872), and brier score (0.006). Tables S3 and S4 show predictors of major cardiac complications in a multivariate model.



**Figure 2. Forest plot and adjusted odds ratio of predictors for 30-day postoperative major cardiovascular complications (myocardial infarction, cardiac arrest, and/or stroke).** ASA indicates American Society of Anesthesiologists Physical Status Classification; ENT-ear, nose, throat; and EVAR-endovascular aneurysm repair.

### Prediction of Postoperative 30-Day Mortality

The mortality risk model with 9 predictors had outstanding AUC (training cohort=0.922, validation cohort=0.925). Figure S3C shows excellent calibration.

Table S5 shows predictors of 30-day mortality in the model.

### Validation of Prediction Model

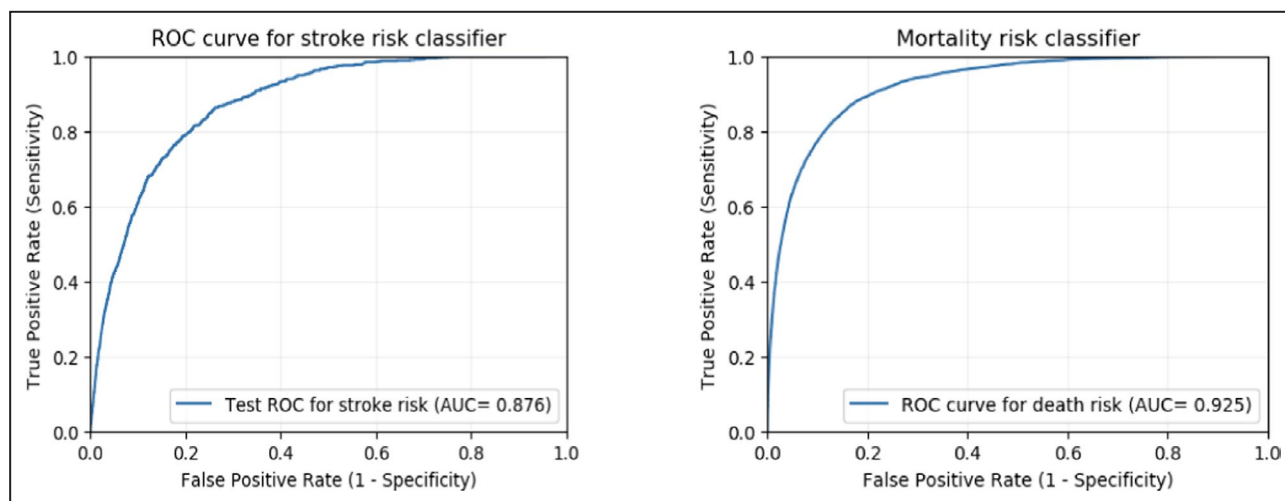
The model derived in the training cohort was validated and tested by applying the model on the validation cohort of 355 870 patients from 2010. Figure 3 shows the model performance (receiver operating characteristic curve) of the validation cohort. The prediction model also used a 5-fold cross validation method for the training cohort from 2007 to 2009. AUC from 5-fold cross validation also showed high predictive performance for major cardiovascular complications (mean AUC, 0.870), stroke (mean AUC, 0.866), cardiac risk (mean AUC, 0.877), and death (mean AUC, 0.922).

### Stroke and Major Cardiac Complications According to Surgery Types

Figure S5 shows the occurrences of 30-day postoperative stroke and cardiac complications (myocardial infarction and stroke) according to surgery types. Vascular (thoracic-EVAR), brain surgery, and carotid endarterectomy had the highest rates of stroke. Open aorta surgery has a higher incidence of stroke compared with EVAR (1.12% versus 0.5%). In regard to cardiac complications, open aorta surgery had the highest risk (4.51%) followed by vascular (thoracic-EVAR, 3.79%; suprainguinal bypass, 3.46%; EVAR, 1.67%), intestinal surgery (1.51%), and liver/pancreas/spleen (1.4%) surgery.

### Practical Application of Risk Model

A probability (%) of 30-day postoperative stroke, major cardiovascular events, and mortality can be calculated using coefficients of predictors from multivariate logistic regression models. Figure 4 shows a web-based risk model. A mobile web-based risk



**Figure 3. Model performance (receiver operating characteristic curve) for stroke and 30-day mortality in the validation group.**

AUC indicates area under the receiver operating characteristic curve.

prediction model was built using a machine learning library, Scikit-Learn (<https://www.predictionmodel.org/>).

Here are 2 examples of the practical application of stroke, the major cardiovascular (myocardial infarction, cardiac arrest, or stroke), cardiac risk (MI, cardiac arrest), and mortality risk calculator in the clinical setting.

A 65-year-old man with a history of coronary artery disease, a history of stroke was admitted to a hospital for emergency hip fracture surgery. The patient has American Society of Anesthesiologists (ASA) physical status class 3, hematocrit 30%, serum sodium 143 mEq/L, serum creatinine 1.5 mg/dL; 30-day postoperative cardiac or stroke risk 3.79%, cardiac risk 2.66%, stroke risk 0.99%, 30-day mortality risk 4.04%.

A 70-year-old woman with a history of stroke, no history of coronary artery disease is scheduled to have elective spine surgery. The patient has ASA physical status class 3, hematocrit 33%, serum sodium 128 mEq/L, serum creatinine 2.5 mg/dL; 30-day postoperative cardiac or stroke risk 3.27%, cardiac risk 2.09%, stroke risk 0.96%, 30-day mortality risk 3.91%.

## DISCUSSION

Our study demonstrated a well-validated prediction model built on 1.16 million patients over 4 years for postoperative stroke, major cardiovascular complications (myocardial infarction, cardiac arrest, or stroke), and death. Although it is well established that stroke is a major complication of surgery with a high

mortality rate,<sup>2,17,19</sup> to our knowledge there are no effective prediction models for individualized estimation of postoperative stroke and cardiac risk. Using 9 clinical variables in a national cohort of patient data from the robust ACS-NSQIP database collected over 4 years, we developed and validated a clinically useful risk assessment model for stroke, cardiac, and mortality risk.

Our stroke predictive model has excellent discriminative ability. Wilcox et al<sup>22</sup> compared existing cardiovascular risk scores in stroke prediction and our model had higher predictive power (AUC, 0.876) for postoperative stroke compared with Gupta MICA (AUC, 0.833), American College of Surgeons surgical risk calculator (AUC, 0.836), Mashour (AUC, 0.773), CHA<sub>2</sub>DS<sub>2</sub>-VASc (AUC, 0.744), and Revised Cardiac Risk Index (AUC, 0.743).<sup>18,22</sup>

Our study found that even small increases of serum sodium level are associated with an increased risk of major cardiovascular complications. Anemia, prior stroke, age, renal dysfunction, and ASA class (class 4 and 5) were also associated with increased risk of postoperative stroke.

In addition to the stroke prediction, our model has excellent major cardiovascular complication prediction (validation AUC, 0.868). History of stroke and coronary artery disease were significant predictors of postoperative cardiovascular complications similar to the Revised Cardiac Risk Index. In the Gupta MICA model, these cardiovascular predictors are not included in the risk calculator.<sup>6</sup> The Gupta MICA and ACS-NSQIP risk calculators do not use history of coronary artery disease such as prior myocardial infarction or angina in their calculators for cardiac complications. We think it is important to include history of coronary artery



### Prediction Model

## Cardiac and Stroke Risk Model

\* 30-day postoperative risk of MI, Cardiac Arrest, Stroke, Mortality

Age,y:

History of Cerebrovascular Disease :  Yes  No

History of Coronary Artery Disease :  Yes  No

ASA Class :

ASA Class 3- Severe disturbance  ASA Class 1  ASA Class 2

Serum Hematocrit $\leq$  27%:  No  Yes

Serum Sodium(mEq/L):  130.1-146  <130.1  >146

Serum Creatinine>1.8mg/dL:  No  Yes

Emergency Surgery :  Yes  No

Surgery Type :

Orthopedic-lower extremity, pelvis  Neuro  Vascular  Thoracic  Abdominal  Urologic  Gynecologic  Pediatric

### Prediction Model

## Result

**30-day Cardiac and/or Stroke Risk: 3.79%**

**30-day Cardiac Risk: 2.66%**

**30-day Stroke Risk: 0.99%**

**30-day Mortality Risk: 4.04%**

\* Cardiac Risk: defined by 30-day postoperative occurrence of myocardial infarction and/or cardiac arrest.

**Figure 4. Mobile web-based cardiac, stroke, mortality risk model.**  
MI indicates myocardial infarction.

disease in the model as coronary artery disease history was shown to be a significant risk factor for future cardiac events.<sup>23</sup>

Renal dysfunction is a significant risk factor for both stroke and major cardiac events in our study. The association with stroke and cardiac complications may be accounted for by the accelerated atherosclerosis associated with renal disease.<sup>24,25</sup> Renal disease was previously reported as a risk factor for perioperative stroke in cardiac surgery.<sup>26</sup>

We differentiated specific types of surgery to further delineate specific risk factors for stroke and cardiac complications. Risk estimates based on the type of procedure are clinically relevant. In terms of stroke risk, brain, and vascular surgery (carotid endarterectomy, aorta, thoracic endovascular aneurysm repair) demonstrate the highest risk. Upper vascular and aortic procedures demonstrate a much higher risk than other lower or peripheral vascular procedures, consistent with prior studies.<sup>27</sup>

Other studies showed preoperative hyponatremia and hypernatremia are associated with significant postoperative mortality and morbidity such as major coronary events, pneumonia, and venous

thromboembolism.<sup>28-30</sup> Anemia is known to be associated with postoperative cardiac events, and increased hematocrit is associated with pulmonary embolism and deep vein thrombosis.<sup>31-33</sup>

In our analysis, a significant proportion of postoperative myocardial infarctions (15.8%), cardiac arrests (10.9%), and strokes (25.0%) occurred after discharge. The Revised Cardiac Risk Index is limited in that the model does not predict the occurrence of cardiac complications after discharge unlike our model.<sup>8,34</sup>

Our model (AUC, 0.789) performs as well as Geriatrics-Sensitive Cardiac Index (AUC, 0.76) in geriatrics population (aged  $\geq$ 65 years) for cardiac risk prediction.<sup>35</sup> In addition, this model has greater predictive ability in postoperative myocardial infarction, stroke, and death (validation AUC, 0.904) compared with Dakik cardiovascular index (AUC, 0.82).<sup>21</sup>

Our study has several strengths. First, a large number of patients were included in the analysis (n=1 165 750) compared with Revised Cardiac Risk Index (n=4315) and Gupta (n=468 795). Second, our study included more recent data over a longer period of time from years 2007 to 2010 compared

with Revised Cardiac Risk Index (years 1989–1994, from single hospital) and Gupta (years 2007–2008).<sup>6,7</sup> Third, our model may help clinicians not only assess the surgical risk but potentially reduce the risk by optimizing serum sodium and hematocrit levels preoperatively, a concept requiring further study. The Revised Cardiac Index, Gupta model, and ACS-NSQIP risk calculator do not include these potentially modifiable risk factors.

Despite its many strengths, this study has some limitations. First, the timing of prior stroke and history of atrial fibrillation are important considerations in risk assessment of stroke before surgery.<sup>36</sup> In addition, new postoperative atrial fibrillation with low rates of anticoagulation initiation within 30 days of discharge, has been found to be associated with increased postoperative risk of stroke after non-cardiac surgery.<sup>37</sup> However, these variables were not included in the model because such information was not available for analysis. We used database analysis from 2007 to 2010 in our study because more recent data did not include history of coronary artery disease, or stroke in the data sets. In conclusion, our study developed a clinically relevant web-based postoperative stroke, major cardiovascular, and mortality risk prediction model. Our model allows for more individualized risk prediction and assessment for postoperative stroke and cardiac complications.

## ARTICLE INFORMATION

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### Sources of Funding

None.

### Disclosures

None.

### Supplementary Material

Tables S1–S5

Figures S1–S5

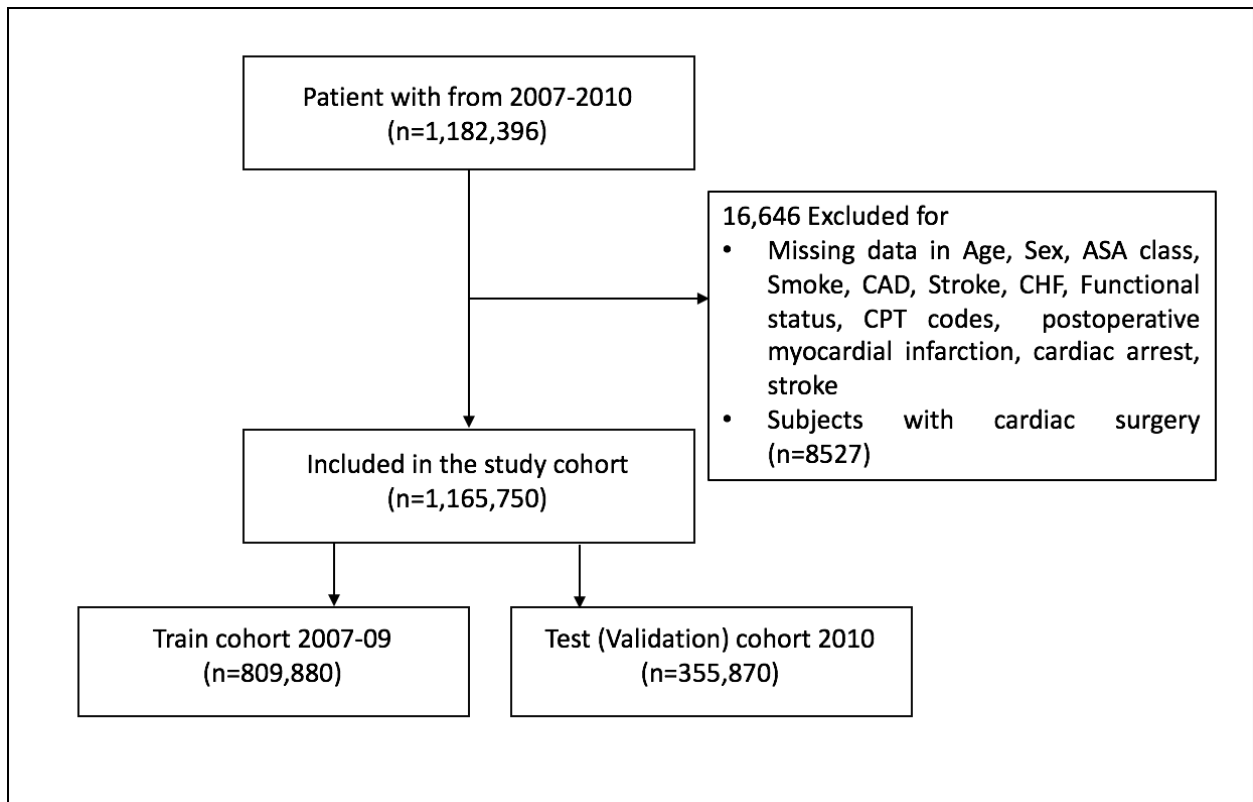
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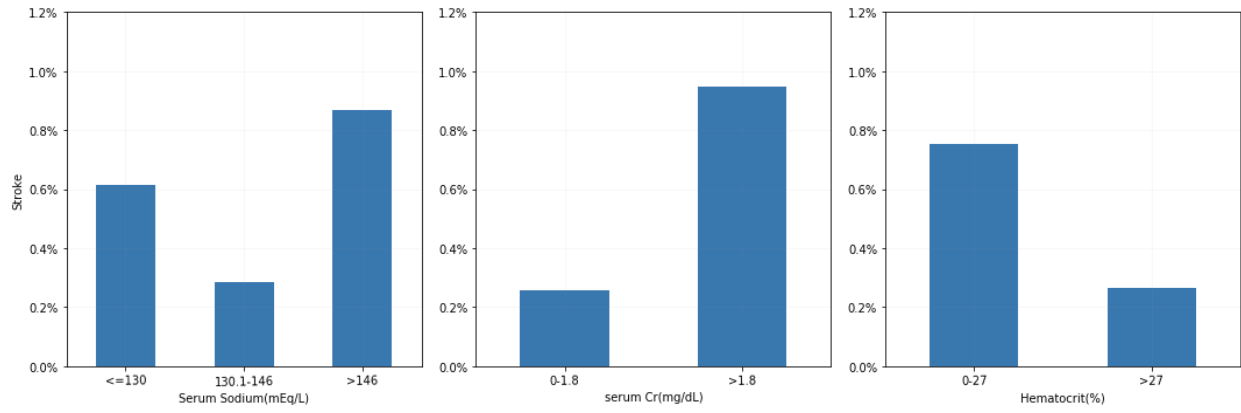
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# **SUPPLEMENTAL MATERIAL**

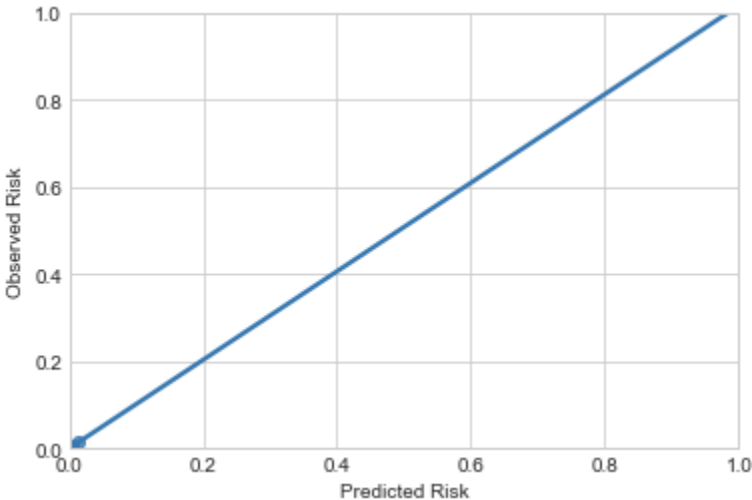
**Figure S1. Participant flow chart.**



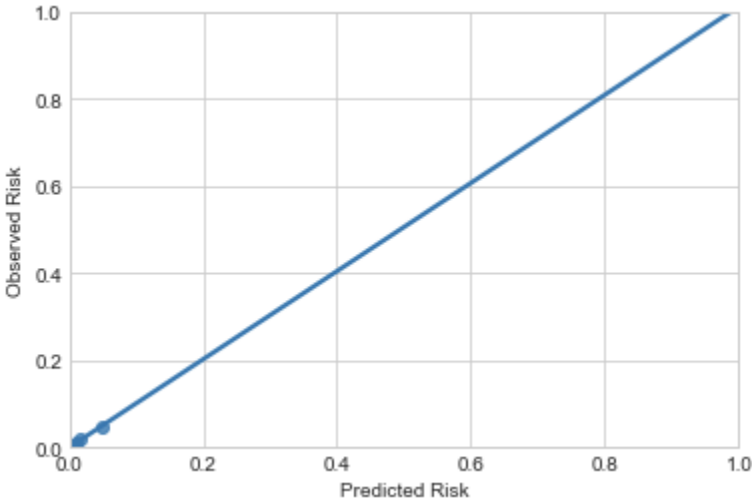
**Figure S2. Postoperative stroke according to serum sodium, creatinine and hematocrit. Stroke rate from 2007-2009 cohort.**



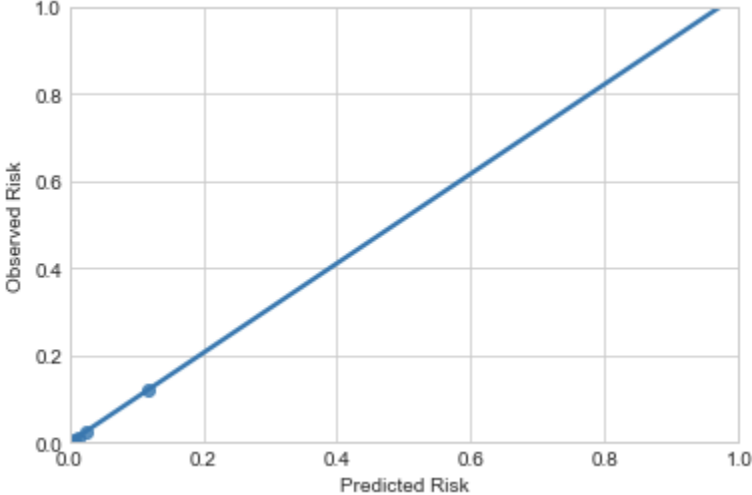
**Figure S3a. Calibration plot for postoperative stroke. Observed vs expected stroke risk.**



**Figure S3b. Calibration plot for postoperative major cardiovascular events(myocardial infarction, cardiac arrest, stroke). Observed vs expected risk.**

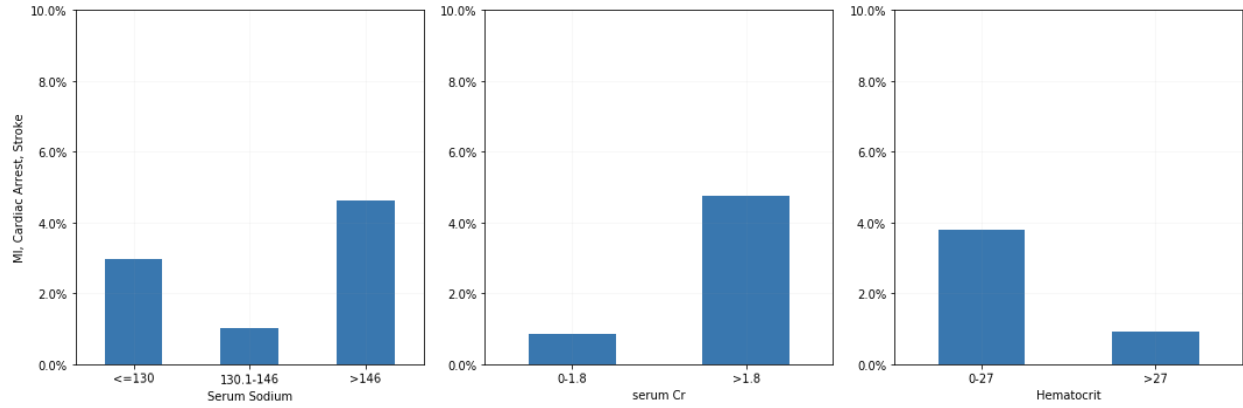


**Figure S3c. Calibration plot for 30-day postoperative death.**

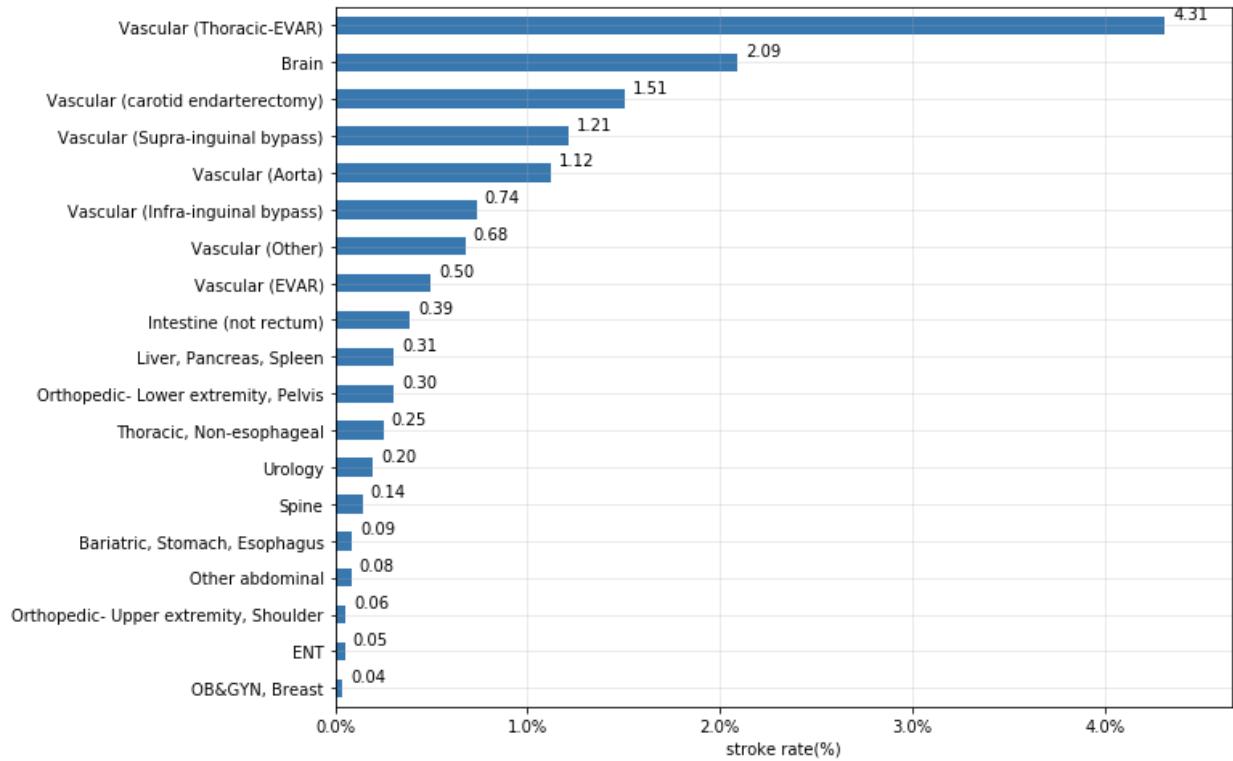


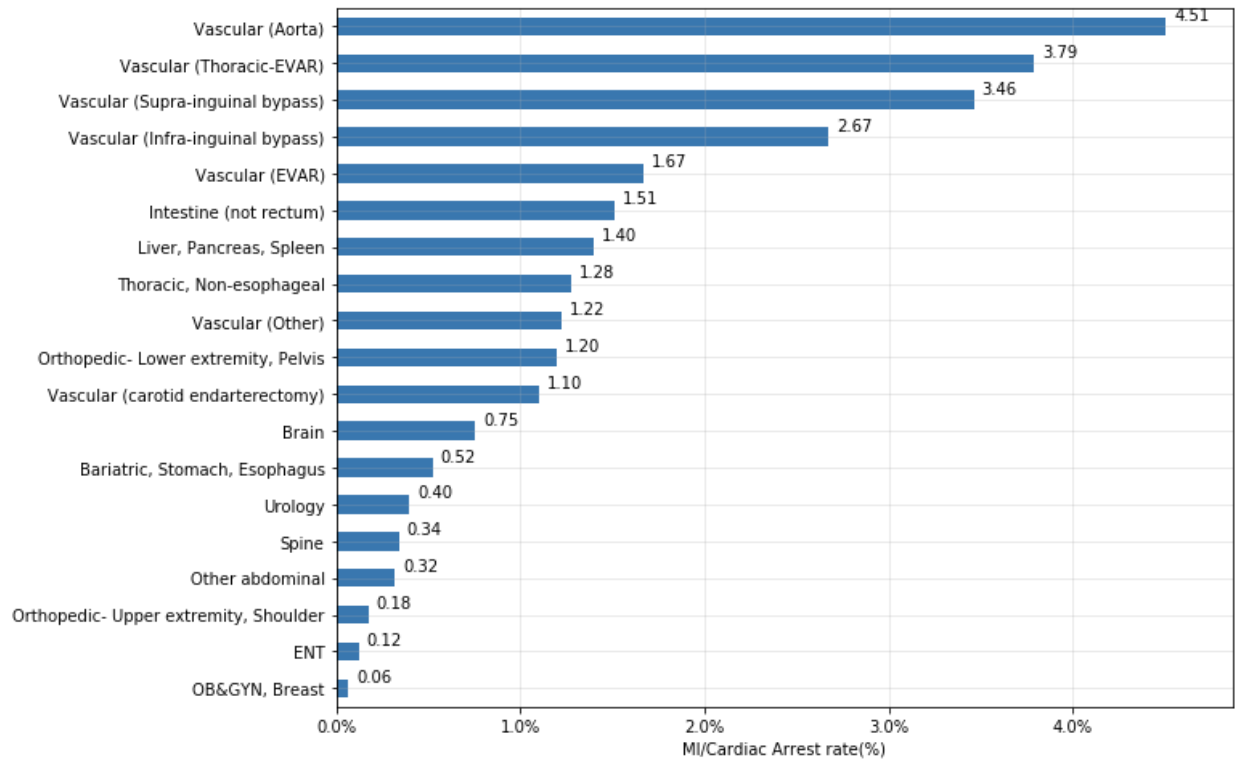


**Figure S4. Postoperative major cardiovascular events (MI, Cardiac Arrest or Stroke) according to serum sodium, creatinine and hematocrit. from 2007-2009 cohort**



**Figure S5. The rates (%) of 30-day postoperative stroke and major cardiac complications in patients according to surgery types.**





**Table S1. Adjusted odds ratio of predictors for 30-day postoperative stroke.**

	Adjusted odds ratio	Coefficient	SE	P-value
Intercept		-10.382	0.366	<0.001
Age (per year)	1.03 (1.02-1.03)	0.026	0.002	<0.001
Stroke	2.3 (2.08-2.55)	0.834	0.052	<0.001
Coronary artery disease	1.02 (0.9-1.15)	0.021	0.062	0.732
Emergency Surgery	1.89 (1.68-2.12)	0.634	0.059	<0.001
Hematocrit 0-27% (ref: >27%)	1.29 (1.08-1.55)	0.255	0.093	0.006
Hematocrit: missing	0.93(0.69-1.26)	-0.071	0.154	0.647
Creatinine >1.8mg/dL (ref:≤1.8)	1.41 (1.24-1.6)	0.343	0.066	<0.001
Creatinine: missing	0.84(0.58-1.23)	-0.171	0.195	0.381
Serum sodium ≤ 130mEq/L (ref: 130.1-146)	1.04 (0.8-1.36)	0.042	0.136	0.755
Serum sodium > 146mEq/L	1.41 (0.99-2.01)	0.346	0.181	0.056
Serum sodium: missing	0.83(0.58-1.21)	-0.181	0.189	0.338
ASA class (ref: ASA 1)				
ASA 2 - mild disturbance	3.48 (1.71-7.08)	1.248	0.362	0.001
ASA 3- severe disturbance	8.51 (4.2-17.25)	2.142	0.360	<0.001

ASA 4- life threatening	14.01 (6.88-28.56)	2.640	0.363	<0.001
ASA 5- moribund	14.71 (6.77-31.93)	2.688	0.396	<0.001
Surgery type (ref: other abdominal surgery)				
ENT	0.71 (0.45-1.13)	-0.337	0.234	0.150
bariatric, stomach, esophagus	0.89 (0.67-1.18)	-0.118	0.147	0.420
brain	11.91 (8.88-15.96)	2.477	0.149	<0.001
intestine (not rectum)	2.18 (1.85-2.57)	0.781	0.083	<0.001
liver, pancreas, spleen	2.41 (1.82-3.19)	0.879	0.143	<0.001
obstetrics, gynecology, breast	0.65 (0.47-0.9)	-0.434	0.168	0.010
orthopedic (lower extremity, pelvis)	1.63 (1.3-2.04)	0.488	0.115	<0.001
orthopedic (upper extremity, shoulder)	0.3 (0.08-1.22)	-1.191	0.710	0.094
spine	1.82 (1.15-2.88)	0.599	0.234	0.010
thoracic (non-esophageal)	1.83 (1.21-2.75)	0.602	0.208	0.004
urology	1.51 (1.03-2.22)	0.414	0.195	0.034
vascular (carotid endarterectomy)	5.19 (4.36-6.17)	1.647	0.089	<0.001
vascular (aorta)	3.08 (2.33-4.06)	1.124	0.141	<0.001
vascular (thoracic EVAR)	15.11 (10.98-20.79)	2.715	0.163	<0.001
vascular (EVAR)	2.17 (1.59-2.96)	0.773	0.159	<0.001

vascular (supra-inguinal)	5.32 (0.72-39.24)	1.671	1.020	0.101
vascular (infra-inguinal)	3.21 (2.59-3.98)	1.167	0.109	<0.001
vascular (other)	3.03 (2.48-3.71)	1.109	0.103	<0.001
other surgery	0.97 (0.66-1.41)	-0.035	0.194	0.856

SE- standard error, CI- confidence interval, EVAR- endovascular aneurysm repair

**Table S2. Adjusted odds ratio of predictors for 30-day postoperative major cardiovascular complications (myocardial infarction, cardiac arrest, and/or stroke).**

	Adjusted odds ratio (95% CI)	Coefficient	SE	P-value
intercept		-9.368	0.224	<0.001
Age (per year)	1.03 (1.03-1.03)	0.027	0.001	<0.001
Stroke	1.46 (1.37-1.55)	0.377	0.031	<0.001
Coronary artery disease	1.43 (1.34-1.52)	0.356	0.031	<0.001
Emergency Surgery	1.88 (1.77-1.99)	0.630	0.031	<0.001
Hematocrit 0-27% (ref: >27%)	1.42 (1.31-1.55)	0.353	0.044	<0.001
Hematocrit: missing	0.91 (0.77-1.08)	-0.097	0.087	0.268
Creatinine >1.8mg/dL	1.96 (1.84-2.09)	0.673	0.032	<0.001
Creatinine: missing	0.78 (0.63-0.97)	-0.249	0.112	0.026
Serum sodium ≤ 130mEq/L (ref: 130.1-146)	1.2 (1.06-1.36)	0.184	0.064	0.004
Serum sodium > 146mEq/L	1.67 (1.42-1.97)	0.515	0.084	<0.001
Serum sodium: missing	0.88 (0.72-1.09)	-0.123	0.107	0.252
ASA class (ref: ASA 1)				
ASA 2 - mild disturbance	3.71 (2.4-5.75)	1.312	0.223	<0.001
ASA 3- severe disturbance	12.01 (7.78-18.54)	2.486	0.221	<0.001

ASA 4- life threatening	25.26 (16.33-39.08)	3.229	0.223	<0.001
ASA 5- moribund	41.62 (26.45-65.51)	3.729	0.231	<0.001
Surgery type				
ENT (ref: other abdominal surgery)	0.56 (0.43-0.72)	-0.582	0.131	<0.001
bariatric, stomach, esophagus	1.3 (1.15-1.47)	0.264	0.061	<0.001
brain	3.74 (2.95-4.74)	1.320	0.121	<0.001
intestine (not rectum)	2.08 (1.92-2.25)	0.733	0.040	<0.001
liver, pancreas, spleen	2.73 (2.4-3.1)	1.003	0.066	<0.001
obstetrics, gynecology, breast	0.36 (0.29-0.45)	-1.008	0.111	<0.001
orthopedic (lower extremity, pelvis)	1.68 (1.51-1.87)	0.520	0.054	<0.001
orthopedic (upper extremity, shoulder)	0.39 (0.22-0.72)	-0.931	0.304	0.002
spine	1.42 (1.1-1.84)	0.354	0.130	0.006
thoracic (non-esophageal)	2 (1.66-2.41)	0.694	0.094	<0.001
urology	1.01 (0.81-1.26)	0.008	0.112	0.944
vascular (carotid endarterectomy)	2.13 (1.92-2.37)	0.758	0.053	<0.001
vascular (aorta)	3.02 (2.65-3.43)	1.104	0.066	<0.001
vascular (thoracic EVAR)	5.27 (4.16-6.67)	1.662	0.120	<0.001
vascular (EVAR)	1.61 (1.37-1.89)	0.476	0.083	<0.001



vascular (supra-inguinal)	2.15 (0.51-9.06)	0.766	0.734	0.297
vascular (infra-inguinal)	2.93 (2.63-3.25)	1.074	0.054	<0.001
vascular (other)	1.58 (1.41-1.77)	0.459	0.058	<0.001
other surgery	1.01 (0.85-1.21)	0.013	0.091	0.890

**Table S3. Adjusted odds ratio of predictors for postoperative Myocardial Infarction or Cardiac Arrest.**

	adjusted odds ratio	coefficient	SE	P-value
Intercept		-9.828	0.283	<0.001
Age (per year)	1.03 (1.03-1.03)	0.027	0.001	<0.001
Stroke	1.19 (1.1-1.28)	0.170	0.037	<0.001
Coronary artery disease	1.58 (1.48-1.69)	0.458	0.035	<0.001
Emergency Surgery	1.85 (1.73-1.98)	0.615	0.035	<0.001
Hematocrit 0-27% (ref: >27%)	1.43 (1.3-1.57)	0.355	0.048	<0.001
Hematocrit: missing	0.93 (0.76-1.13)	-0.075	0.102	0.462
Serum creatinine >1.8mg/dL (ref:≤1.8)	2.13 (1.99-2.29)	0.758	0.036	<0.001
Serum creatinine: missing	0.74 (0.57-0.96)	-0.297	0.133	0.025
Serum sodium ≤ 130mEq/L (ref: 130.1-146)	1.23 (1.07-1.41)	0.205	0.071	0.004
Serum sodium > 146mEq/L	1.69 (1.41-2.02)	0.525	0.092	<0.001
Serum sodium: missing	0.95 (0.74-1.22)	-0.048	0.126	0.702
ASA class (ref: ASA 1)				
ASA 2 - mild disturbance	4.02 (2.31-7)	1.391	0.283	<0.001
ASA 3- severe disturbance	14.55 (8.39-25.22)	2.678	0.281	<0.001

ASA 4- life threatening	33.26 (19.14-57.79)	3.505	0.282	<0.001
ASA 5- moribund	58.15 (32.96-102.6)	4.063	0.290	<0.001
Surgery type (ref: other abdominal surgery)				
ENT	0.49 (0.36-0.68)	-0.704	0.159	<0.001
bariatric, stomach, esophagus	1.42 (1.25-1.62)	0.352	0.067	<0.001
brain	1.18 (0.76-1.83)	0.164	0.224	0.466
intestine (not rectum)	2.04 (1.87-2.23)	0.714	0.045	<0.001
liver, pancreas, spleen	2.82 (2.44-3.25)	1.036	0.073	<0.001
obstetrics, gynecology, breast	0.27 (0.2-0.36)	-1.312	0.146	<0.001
orthopedic (lower extremity, pelvis)	1.68 (1.49-1.89)	0.520	0.060	<0.001
orthopedic (upper extremity, shoulder)	0.41 (0.21-0.8)	-0.884	0.336	0.009
spine	1.3 (0.96-1.75)	0.259	0.154	0.094
thoracic (non-esophageal)	2.02 (1.65-2.48)	0.705	0.104	<0.001
urology	0.84 (0.64-1.1)	-0.175	0.137	0.202
vascular (carotid endarterectomy)	1.16 (1.01-1.34)	0.152	0.073	0.037
vascular (aorta)	2.95 (2.56-3.4)	1.082	0.073	<0.001
vascular (thoracic EVAR)	2.64 (1.89-3.68)	0.969	0.171	<0.001

vascular (EVAR)	1.47 (1.22-1.77)	0.387	0.095	<0.001
vascular (supra-inguinal)	1.29 (0.17-9.53)	0.255	1.020	0.803
vascular (infra-inguinal)	2.83 (2.52-3.19)	1.041	0.060	<0.001
vascular (other)	1.23 (1.08-1.41)	0.209	0.070	0.003
other surgery	1.02 (0.84-1.24)	0.020	0.101	0.846

**Table S4. Adjusted odds ratio of predictors for postoperative Myocardial Infarction.**

	Adjusted odds ratio	Coefficient	SE	P value
Intercept	0 (0-0)	-11.330	0.457	<0.001
Age (per year)	1.04 (1.04-1.04)	0.040	0.002	<0.001
Stroke	1.23 (1.1-1.36)	0.204	0.054	<0.001
Coronary artery disease	2.03 (1.84-2.23)	0.708	0.049	<0.001
Emergency Surgery	1.74 (1.57-1.94)	0.557	0.054	<0.001
Hematocrit 0-27% (ref: >27%)	1.19 (1.01-1.4)	0.171	0.084	0.041
Hematocrit: missing	0.81 (0.60-1.1)	-0.213	0.156	0.172
Serum creatinine >1.8mg/dL (ref:≤1.8)	1.66 (1.48-1.86)	0.506	0.058	<0.001
Serum creatinine: missing	0.87 (0.60-1.26)	-0.142	0.189	0.452
Serum sodium ≤ 130mEq/L (ref: 130.1-146)	1.09 (0.86-1.38)	0.087	0.119	0.464
Serum sodium > 146mEq/L	1.14 (0.81-1.61)	0.132	0.175	0.452
Serum sodium: missing	0.91 (0.64-1.3)	-0.095	0.181	0.599
ASA class (ref: ASA 1)				
ASA 2 - mild disturbance	4.19 (1.72-10.21)	1.433	0.454	0.002
ASA 3- severe disturbance	12.01 (4.95-29.12)	2.486	0.452	<0.001

ASA 4- life threatening	20.32 (8.35-49.45)	3.012	0.454	<0.001
ASA 5- moribund	22.22 (8.79-56.17)	3.101	0.473	<0.001
Surgery type (ref: other abdominal surgery)				
ENT	0.39 (0.23-0.67)	-0.940	0.274	0.001
bariatric, stomach, esophagus	1.39 (1.12-1.72)	0.328	0.109	0.003
brain	1.1 (0.52-2.33)	0.095	0.384	0.806
intestine (not rectum)	2.1 (1.83-2.42)	0.743	0.071	<0.001
liver, pancreas, spleen	2.36 (1.86-3)	0.859	0.122	<0.001
obstetrics, gynecology, breast	0.31 (0.21-0.47)	-1.165	0.205	<0.001
orthopedic (lower extremity, pelvis)	1.85 (1.55-2.22)	0.616	0.092	<0.001
orthopedic (upper extremity, shoulder)	0.21 (0.05-0.86)	-1.539	0.710	0.030
spine	1.59 (1.05-2.41)	0.464	0.212	0.029
thoracic (non-esophageal)	1.64 (1.15-2.33)	0.495	0.179	0.006
urology	1.2 (0.85-1.69)	0.183	0.175	0.294
vascular (carotid endarterectomy)	1.64 (1.36-1.99)	0.497	0.098	<0.001
vascular (aorta)	3.46 (2.79-4.29)	1.242	0.109	<0.001
vascular (thoracic EVAR)	2.11 (1.18-3.79)	0.748	0.298	0.012

vascular (EVAR)	2.25 (1.77-2.86)	0.810	0.123	<0.001
vascular (supra-inguinal)	4.02 (0.55-29.59)	1.392	1.018	0.171
vascular (infra-inguinal)	4.13 (3.5-4.87)	1.417	0.084	<0.001
vascular (other)	1.28 (1.02-1.59)	0.243	0.112	0.030
other surgery	0.75 (0.52-1.08)	-0.285	0.186	0.125

**Table S5. Adjusted odds ratio of predictors for 30-day mortality.**

	Adjusted odds ratio	Coefficient	SE	P-value
Intercept		-9.700	0.204	<0.001
Age (per year)	1.04 (1.04-1.04)	0.039	0.001	<0.001
Stroke	1.18 (1.12-1.24)	0.165	0.026	<0.001
Coronary artery disease	1.01 (0.96-1.07)	0.013	0.026	0.632
Emergency Surgery	2.77 (2.66-2.89)	1.019	0.022	<0.001
Hematocrit 0-27% (ref: >27%)	1.78 (1.68-1.89)	0.578	0.030	<0.001
Hematocrit: missing	0.75 (0.64-0.88)	-0.288	0.08	<0.001
Serum creatinine >1.8mg/dL	2.14 (2.04-2.24)	0.759	0.024	<0.001
Serum creatinine: missing	0.77 (0.63-0.93)	-0.265	0.100	0.008
Serum sodium ≤ 130mEq/L (ref: 130.1-146)	1.62 (1.49-1.76)	0.481	0.043	<0.001
Serum sodium > 146mEq/L	2.25 (2-2.53)	0.811	0.059	<0.001
Serum sodium: missing	0.82 (0.68-1.00)	-0.194	0.097	0.047
ASA class (ref: ASA 1)				
ASA 2 - mild disturbance	2.74 (1.83-4.1)	1.008	0.205	<0.001
ASA 3- severe disturbance	15.01 (10.1-22.31)	2.709	0.202	<0.001



ASA 4- life threatening	59.93 (40.29-89.13)	4.093	0.203	<0.001
ASA 5- moribund	261.22 (174.15-391.83)	5.565	0.207	<0.001
Surgery type (ref: other abdominal surgery)				
ENT	0.29 (0.22-0.38)	-1.231	0.135	<0.001
bariatric, stomach, esophagus	1.14 (1.05-1.24)	0.132	0.044	0.003
brain	1.99 (1.62-2.43)	0.687	0.103	<0.001
intestine (not rectum)	1.76 (1.67-1.86)	0.567	0.028	<0.001
liver, pancreas, spleen	1.8 (1.62-2)	0.588	0.053	<0.001
obstetrics, gynecology, breast	0.23 (0.19-0.28)	-1.466	0.104	<0.001
orthopedic (lower extremity, pelvis)	1.13 (1.04-1.22)	0.120	0.040	0.002
orthopedic (upper extremity, shoulder)	0.41 (0.27-0.6)	-0.904	0.202	<0.001
spine	0.72 (0.56-0.93)	-0.324	0.128	0.012
thoracic (non-esophageal)	2.03 (1.8-2.3)	0.709	0.063	<0.001
urology	0.41 (0.33-0.52)	-0.890	0.115	<0.001
vascular (carotid endarterectomy)	0.46 (0.41-0.51)	-0.784	0.060	<0.001
vascular (aorta)	1.45 (1.31-1.61)	0.372	0.053	<0.001
vascular (thoracic EVAR)	1.14 (0.88-1.49)	0.135	0.133	0.313
vascular (EVAR)	0.63 (0.54-0.73)	-0.465	0.074	<0.001

vascular (supra-inguinal)	0.68 (0.19-2.45)	-0.386	0.654	0.555
vascular (infra-inguinal)	1 (0.91-1.1)	0.002	0.049	0.962
vascular (other)	0.82 (0.76-0.9)	-0.193	0.045	<0.001
other surgery	0.85 (0.74-0.96)	-0.168	0.065	0.009