Development and internal validation of models to predict time-to-event for major medical complications within 30-days after planned colectomy: a retrospective population cohort study

Study Protocol

Principal Investigators

Cox proportional hazards analysis paper:

Dr. Alana Flexman, MD, FRCPC
Clinical Associate Professor, Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia (UBC)
Department of Anesthesia, Providence Health Care

Dr. Xue Chen (Janny) Ke, MD, FRCPC
Anesthesiologist, Department of Anesthesia, St. Paul's Hospital
Clinical Instructor, Department of Anesthesiology, Pharmacology & Therapeutics, UBC; Adjunct, Department of Anesthesia, Pain Management & Perioperative Medicine, Dalhousie University

Machine learning analysis paper:

Dr. Matthias Görges, PhD
Assistant professor, Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia; Research Institute, BC Children’s Hospital

Co-Investigators

Dr. Rama Sreepada, PhD
Postdoctoral research fellow, Department of Anesthesiology, Pharmacology & Therapeutics, UBC; Research Institute, BC Children’s Hospital

Dr. Long Ngo, PhD
Associate Professor, Department of Biostatistics, Harvard School of Public Health
Division of General Medicine, Beth Israel Deaconess Medical Center
Harvard Medical School

Sihaoyu (Sherry) Gao, PhD Candidate
Department of Statistics, Faculty of Science, UBC

Dr. Lang Wu, PhD
Professor, Department of Statistics, Faculty of Science, UBC

Dr. Stephan Schwarz, MD, FRCPC
Professor, Department of Anesthesiology, Pharmacology & Therapeutics, UBC;
Department of Anesthesia, Providence Health Care

Dr. Carl Brown, MD, MSc, FRCSC
Head, Division of General Surgery, St. Paul’s Hospital; Clinical Assistant Professor, Department of Surgery, Faculty of Medicine, UBC; Chair, Section of Colorectal Surgery, UBC; Provincial Lead for Surgical Oncology, BC Cancer Agency

Jeff Rueger, Patient Partner

Primary Contact: Dr. Xue Chen (Janny) Ke jannyke@alumni.ubc.ca
Development and internal validation of models to predict time-to-event for major medical complications within 30-days after planned colectomy: a retrospective population cohort study

Introduction
Planned (elective or time sensitive) colectomy are performed for indications including cancer, inflammatory bowel disease (IBD), and diverticulitis (1,2). After colectomy, patients are at risk of a variety of major medical complications, including pneumonia, myocardial infarction (MI), cerebral vascular event (CVA), venous thromboembolism (VTE), acute renal failure (ARF), and sepsis (2,3). However, different complications tend to happen at different times after surgery. Accurate risk prediction, not only whether a complication may occur in a patient, but also when, is crucial for patient education, monitoring, and disposition planning. While several studies have explored the incidence and binary risk prediction for major complications after surgeries (1–3), there has been scarce literature on time-to-complication prediction modeling in recent population cohort data.

Objectives
1. Develop and internal validate Cox proportional hazards models to predict time-to-complication for each individual major medical complication captured in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) dataset (pneumonia, myocardial infarction (MI), cerebral vascular event (CVA), venous thromboembolism (VTE), acute renal failure (ARF), and sepsis) or adverse outcomes (mortality, readmission), that started within 30-days after elective colectomy.
2. Develop and internal validate machine learning models to predict time-to-complication for major medical complications and adverse outcomes (same as in objective 1) within 30-days after elective colectomy in NSQIP. The best machine learning model for each complication will be compared to the Cox proportional hazards model in terms of discrimination, and calibration.

Methods
Following approval from the University of British Columbia Clinical Research Ethics Board with waived informed consent, we will conduct a time-to-event survival analysis in a retrospective cohort using NSQIP®, a prospectively-collected multicentre dataset with more than 150 clinical variables within 30 days after surgery (4). This dataset includes information on whether the patient was diagnosed with major complications (in- or out-of-hospital) as well as the number of postoperative days to the diagnoses of complications, as defined by a standardized criteria within the NSQIP operations manual (4). The general dataset will be linked with the NSQIP® Procedure Targeted Colectomy dataset, which contains additional colectomy-specific variables. The study will be pre-registered prior to data analysis (Clinicaltrials.gov) and reported according to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines and Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research (5).
**Study Population**

The study will include all patients who are 18 years or older undergoing elective colectomy, whose data has been collected in the NSQIP® Procedure Targeted Colectomy dataset from 2014-2019, inclusively. The estimated sample size is approximately 130,000 patients.

We will exclude patients with American Society of Anesthesiologists (ASA) Physical Status (PS) V (defined as “5-Moribund”) (ASA PS 6 - organ donation is not included within NSQIP). We will also exclude patients who are undergoing urgent or emergency surgery, or have indication for colectomy consisting of “Acute diverticulitis”, “Enterocolitis (e.g. C. Difficile)”, and “Volvulus” due to the non-elective nature of these pathologies. Patients with disseminated cancer, wound infection (i.e. potentially recent surgery), systemic sepsis, or ventilator-dependence preoperatively will also be excluded.

**Model Prediction Endpoints**

We will create a distinct time-to-event prediction model for each of the following new postoperative complications or adverse outcomes within 30 days postoperatively:

- Major medical complications: pneumonia, myocardial infarction (MI), cerebral vascular event (CVA), venous thromboembolism (VTE), acute renal failure (ARF), and sepsis or septic shock
- Adverse outcomes: mortality, readmission

The definitions of the complications, outcomes, and time-to-complication date criteria collected from NSQIP variables are included in Appendix 1 (Data Extraction Form).

**Candidate predictors**

To predict time-to-complication, we selected candidate predictors from the NSQIP variables based on literature and clinical experience, and obtained consensus within our multidisciplinary team. For generalizability and future external validation, we selected predictors that are routinely collected in hospital electronic health records (EHRs) such as at our institution whenever possible. Candidate predictors are as follows (please see Appendix 1 for detailed definitions):

- Age, sex, race, body mass index (BMI)
- ASA, diabetes, smoker within one year preoperatively, severe obstructive chronic pulmonary disease (COPD), ascites, congestive heart failure (CHF), hypertension on medications, preoperative renal failure (acute renal failure, dialysis, and/or glomerular filtration rate (GFR) <60 based on preoperative creatinine), preoperative functional status, dyspnea, coagulopathy
- Steroid and/or immunosuppressant use preoperatively
- Chemotherapy within 90 days preoperatively
- Primary indication for colectomy (recategorized as):
  - Cancer
  - Non-malignant polyp
  - Inflammatory bower disease (IBD)
  - Diverticulitis
  - Bleeding
  - Other
- Surgical approach: minimally invasive vs. open
- Total operation time
- Use of regional anesthesia as an additional anesthetic technique (epidural, peripheral, spinal)
- Wound classification (end of surgery)
For the two models to predict time-to-event for adverse outcomes (mortality and readmission), we will perform sensitivity analysis to determine whether including the occurrence of any major complications (pneumonia, myocardial infarction (MI), cerebral vascular event (CVA), venous thromboembolism (VTE), acute renal failure (ARF), and sepsis) as individual predictors improve discrimination and calibration.

**Statistical Analysis**

1. **Preprocessing**
   - Convert age from the NSQIP character variable to continuous variable, with Age “90+” recoded as 90
   - Standardizing the coding of missing values: missing coded in NSQIP as “-99”, “unknown”, “None Assigned”, or “NULL”. Each variable will be individually examined to ensure that the missing value is correctly standardized.
   - Pre-processing variables for survival analysis: creation of a censored 1 vs. 0 variable for each outcome to be modelled based on time-to-event and the occurrence of complications.
   - Missing values
     - Missing values for candidate predictors will be quantified. If the % missing is:
       1. >10% then exclude the predictor from the model
       2. <1% then delete (complete case analysis)
       3. >=1% and <10% then multiple imputation by chained equations (time-to-event variables are never imputed)
     - Note that patients with missing values for complications will be coded as zero for the complication (i.e. assumed to not have the complication), as the presence of complications would have been in the health records
     - The % missing data for height and weight will be examined in cohort characteristics. If <1% is missing, then BMI will be calculated using these variables.
     - Patients with a complication or adverse event but missing time-to-event data will be excluded from modeling. The extent of bias (i.e. if these patients have different cohort characteristics compared to patients without missing time-to-event data) will be assessed in sensitivity analysis. Note that it is expected for patients without a complication or adverse event to have missing time-to-event data, thus these patients are not excluded.
     - Check collinearity with variance inflation factor and Pearson’s correlation coefficient: if present, combine information from collinear variables if feasible (e.g. new variables is “yes” if any of the variables it aggregates are “yes”), otherwise eliminate the variable that has more missing values or would be less accurately ascertained
     - Techniques for class imbalance: e.g. resampling within the derivation set to improve model performance in the case of rare outcomes

2. **Descriptive statistics**
   - Cohort characteristics will be stratified by mortality, by each complication and by derivation vs. validation sets (please see list below). Continuous variables will be presented as mean (standard deviation) and median (IQR) for parametric and nonparametric data, respectively. Categorical variables will be
presented as frequency (%). For comparison amongst groups, ANOVA will be used for parametric data, Kruskal-Wallis for nonparametric data, and Chi-square tests for categorical data. Standardized mean difference will be presented. Exploratory visualizations will be performed.

- Distribution of time to complication data (time to any complication, and time to each complication): failure curves, i.e. plotting the 1-S(t) (survival function) to determine the risk of complication daily within 30 days
- Exploratory analysis for complications that tend to occur concurrently or are associated with each other

3. Model building
- Models will be created using the entire dataset and using bootstrap validation
  - Individual models will be built for each outcome.
  - Assumptions for the Cox model will be checked prior to model building, including but not limited to:
    1. Proportionality: visual inspection of the Kaplan-Meier curves, Log Log S(t) test, Schoenfeld residuals. If these assumptions hold, we will use the Cox proportional hazards (CPH) modeling; if not, we will use the accelerated failure time (AFT) modeling.
    2. Competing risk: complications are assumed to be independent from each other. If mortality is >10%, it will be modeled as a competing risk (however, we do not anticipate mortality to be >10% for elective colectomy).
- Sensitivity analyses
  1. After examining the temporal distributions of events, we may include complications that tend to happen earlier as predictors for complications that happen later, and may be related to earlier complications
  2. For the two models to predict time-to-event for adverse outcomes (mortality and readmission), we will perform sensitivity analysis to determine whether including the occurrence of major complications (pneumonia, myocardial infarction (MI), cerebral vascular event (CVA), venous thromboembolism (VTE), acute renal failure (ARF), and sepsis) as predictors improve discrimination and calibration
  3. Restricted cubic splines for continuous predictors (age, BMI, duration of surgery) to explore non-linear relationships
  4. Compare cohort characteristics for patients with a complication or adverse event but missing time-to-event data, vs. patients without missing time-to-event data, to evaluate for the impact of bias from the exclusion of patients with missing time-to-event data
- Additional analysis will be performed to improve time-to-event predictions, including but limited to:
  1. Accelerated failure time (AFT) modeling to directly model failure time. Compared to CPH, AFT is more interpretable and robust with omitted predictor variables.
  2. Machine learning models that can facilitate time-to-event predictions: including but not limited to boosting trees, neural networks.

4. Model evaluation, with bootstrapped 95% confidence intervals and optimism
5. Sample size calculation

- We used the PMSampsize package in R and followed guidance specifically for time-to-event multivariable modeling (6). Based on an event rate of 0.01 over 30 days (i.e. 0.00033333 per patient per day in the study period totalling 30 days), Cox-Snell R-squared 0.11 (the maximum for the event rate of 0.01 over 30 days) (6), 0.05 acceptable difference in apparent & adjusted R-squared, shrinkage 0.9, a minimum of 51 events (5091 patients, 15,2730 person-days of follow-up) are required for modeling with 30 predictor variables.

Data will be analyzed using R and/or Python.

List of variables in cohort characteristics (Please see Appendix 1 for details)

**Preoperative and intraoperative variables:**
- Age, sex, race, height, weight, body mass index (BMI)
- ASA, diabetes, smoker within one year preoperatively, severe obstructive chronic pulmonary disease (COPD), ascites, congestive heart failure (CHF), hypertension on medications, preoperative renal failure (acute renal failure, dialysis, and/or GFR <60 based on preoperative creatinine), preoperative functional status, dyspnea, coagulopathy
- Steroid/immunosuppressant use preoperatively
- Chemotherapy within 90 days preoperatively
- Primary indication for colectomy (categorized and full list)
- Surgical approach: minimally invasive vs. open (categorized and full list)
- Total operation time
- Use of regional anesthesia as an additional anesthetic technique (epidural, peripheral, spinal)
- Wound classification (end of surgery)

**Postoperative variables:**
- Myocardial infarction
- Stroke/CVA
- VTE (composite: pulmonary embolism, DVT)
- Pneumonia
- Acute renal failure
- Sepsis or septic shock (composite of systemic sepsis and septic shock)
- Readmission: also present % unplanned
- Mortality
- Complication or death (composite of the major complications modeled)
- Time to first complication or death (composite of the major complications modeled)
- Wound issues (composite: superficial and deep infection, wound disruption)
- Non-home discharge
- Bleeding requiring transfusion
- Anastomotic leak
- Prolonged postoperative ileus (nothing by mouth or nasogastric tube)
- Urinary tract infection
- Transfusion (packed red blood cell (PRBC) within the first 72 hours of surgery start time)
- Cardiac Arrest Requiring cardiopulmonary resuscitation (CPR)
- On ventilator >48h postoperatively
- Still in Hospital > 30 Days
- Unplanned reoperation
References


