Development and internal validation of models involving vital signs to predict troponin level and myocardial injury after noncardiac surgery: a single-centre retrospective cohort study

Protocol

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Introduction

The incidence of myocardial injury after noncardiac surgery (MINS) is approximately 12-15% and is associated with an increased risk of 30-day mortality (1), 1-year mortality (2), and 2-year major vascular events (3). Since more than 90% of patients with MINS are asymptomatic, routine troponin monitoring is required for detection (4). The postoperative days 0, 1, and 2 accounts for approximately 40%, 40%, and 10% of MINS, respectively (4). Presently, the Canadian Cardiovascular Society (CCS) perioperative guidelines recommend patients identified to be at risk according to the Revised Cardiac Risk Index (RCRI) and BNP/NT-proB-type Natriuretic Peptide (NT-proBNP) receive daily postoperative troponin monitoring for three days to identify MINS events (5). European and American societies have similar recommendations for troponin monitoring to detect MINS (6).

Current risk stratification models have multiple limitations (4). Most importantly, they predict an elevated risk over the postoperative period but cannot pinpoint when MINS may happen in the postoperative course given the patients' changing condition. Moreover, prescription of troponin monitoring is not universal (7), infrequent and inconsistent troponin monitoring may lead to delayed detection and management, and the rise of troponin is delayed by 3-4 hours from the time of injury (4).

Retrospective cohort studies show association amongst intraoperative and postoperative derangements in vital signs and MINS (4). Vital signs are routinely available within the electronic medical record, and may serve as objective predictors (i.e. as opposed to free text and disease names that have higher risks of misclassification and errors). Using both traditional longitudinal analysis techniques and novel methods in machine learning, we will investigate whether intraoperative and postoperative vital signs can enhance MINS surveillance by providing temporal prediction of MINS events.

Table 1. Preoperative factors studied in literature associated with MINS and/or major myocardial complication and mortality

Variable	References
Age	Goldman 1977 (8), Lee 1999 (9), Kheterpal 2009 (10), Botto 2014 (11), House 2016 (12)
Congestive heart failure	Lee 1999, Botto 2014
Coronary artery disease	Lee 1999, Kheterpal 2009, Botto 2014
Cerebrovascular disease	Lee 1999, Kheterpal 2009, Botto 2014

Peripheral vascular disease	Botto 2014
Diabetes	Lee 1999 (Insulin-dependent), Botto 2014 (though not found to be predictive in Kheterpal 2009)
RCRI	Lee 1999
Hypertension	Kheterpal 2009 (hypertension requiring medication), Botto 2014, Ruetzler 2020 (4)
Kidney function (laboratory)	Lee 1999, Botto 2014 (though not found to be predictive in Kheterpal 2009)
BNP / NT-proBNP	Choi 2010 (13), Rodseth 2013 (14) and 2014 (15) metanalyses, Malhotra 2016 (16), Duceppe 2020 (17)
Anemia	Feng 2017 (18)
Heart rate	Abbott 2016 (>96) (19), Laitio 2004 (increased variability) (20), Devereaux 2011 (every increase by 10 from baseline) (21)
American Society of Anesthesiologist physical status	House 2016

Table 2. Intraoperative factors studied in literature associated with MINS and/or major myocardial complication and mortality

Variable	**References**
Type and risk of surgery (various definitions)	Lee 1999, Boersma 2005 (22), Davenport 2007 (23) Not found to be predictive in Kheterpal 2009 likely due to different definitions and study populations.
Emergency surgery	Detsky 1986 (24), Boersma 2005, Kheterpal 2009, Botto 2014, House 2016, Zhao 2017 (25), House 2016 Emergency surgery patients excluded in RCRI (Lee 1999)
Red blood cell (RBC) transfusion	Kheterpal 2009, Whitlock 2015 (26), Wu 2010 (27), Glance 2011 (28), Devereaux 2011

Hypotension (mmHg)	Wesselink 2018 (29), Sessler 2018 (30)
Tachycardia (beats)	House 2016 (>100 beats for >59 minutes), Abbott 2018 (>100)

Table 3. Postoperative factors studied in literature associated with MINS and/or major myocardial complication and mortality

Variable	**References**
Postoperative hypotension	van Lier 2018 (quartiles, 3 days postoperatively) (31), Sessler 2018 (<90mmHg, 4 days postoperatively) Liem 2020 (duration MAP <75, 24 hours postoperatively) (32)
Acute kidney injury	Zhao 2017
Vasopressor use 24 hours after surgery	Zhao 2017

Objectives

1. To develop and internally validate a model that uses the duration and degree of intraoperative and postoperative hypotension to predict the daily maximum troponin level from postoperative days zero to two, in a high risk population where troponin monitoring was ordered.
2. To develop and internally validate a model that uses the duration and degree of intraoperative and postoperative hypotension to predict daily probability of MINS or death (binary outcome, according to the 2021 American Heart Association (AHA) definitions (6) from postoperative days zero to two.
3. To evaluate how different definitions of hypotension affect the primary and secondary models above, and analyze the intraoperative and postoperative hypotension separately to determine whether intraoperative or postoperative hypotension alone are sufficient for prediction.
4. To explore whether other intraoperative and postoperative vital sign information (heart rate, oxygen saturation, and end-tidal carbon dioxide derangements at various definitions) add predictive value to the primary and secondary models above.
5. To use machine learning methods to perform exploratory analysis to determine 1) optimal methods for imputation for time series data; 2) visualization of time series data in the setting of prediction; 3) development and internal validation of machine learning models to use the time series data to predict troponin levels; and 4) to determine how many hours earlier than a binary MINS diagnosis were vital signs able

to predict a MINS diagnosis (as determined by when in the time series prior to MINS diagnosis that the model achieved various thresholds of predicted probability).

Methods

This is a single-center, retrospective cohort study on the development and internal validation of a prediction model.

Population

This study will include patients aged 45 years and older undergoing inpatient noncardiac surgery, who had MINS protocol ordered for postoperative high sensitivity troponin monitoring based on the CCS guidelines (5) from January 2020 to June 2021 (estimated sample size of 750, event rate of ~75).

Patients will be excluded if they do not have intraoperative and postoperative vital signs, or any postoperative troponin measurements. Patients who underwent repeat surgery or were readmitted within the first 72 hours postoperatively will be excluded, since patients who are discharged and readmitted will not have vital measurements as outpatients. If a patient had multiple admissions where the MINS protocol was ordered, only the first inpatient admission will be included. Patients who had positive troponin on postoperative day 4 will be excluded, since vital signs are only included up to postoperative day 3 for consistency.

Data sources

Following research ethics board approval, data will be extracted from Cerner Surginet Anesthesia (intraoperative electronic records) and Cerner PowerChart (preoperative and postoperative electronic records). The extracted data will consist of cohort characteristics (patient, anesthetic, surgical variables relevant to MINS (see Data Dictionary below), and patient vital signs with time stamps up to postoperative day 3. The time series time stamps will be transposed to have the start of surgery as 00:00, Jan 1, 2020. A manual chart review will also be performed to extract data not automatically retrieved from Cerner and Surginet (e.g. diagnoses of morbidities). We will extract relevant preoperative comorbidities, including RCRI and Charleson Comorbidity Index categories that are available to the Cerner team via CIHI with no date limit to obtain all preoperative comorbidities (please see Appendix). The Cerner, Surginet, and chart review data will then be linked by de-identified study ID and full surgery date.

Duration of data collection

Preoperative laboratory values are collected within 30 days before surgery. Preoperative vitals are collected within 24 hours before surgery. The total duration of subsequent data collection will be from the time of surgery up to postoperative day 3 (since the MINS protocol monitors for 3 days) or hospital discharge or death, whichever occurs first. Since 90% of MINS happen between postoperative days zero and two (4) and the frequency of monitoring would likely decrease by postoperative day 3, we will model troponin from postoperative day 0 to postoperative day 2 for the primary analysis to balance utility of the temporal model and prediction data quality.

Outcome

In the primary model, we will model high-sensitivity troponin (hsTnT) level as a continuous outcome, such that the model will remain useful if the troponin threshold definitions for MINS evolve.

In the secondary model, we will use the American Heart Association (AHA) definitions (6) for MINS, briefly:

1. Postoperative hsTnT 20 to <65 ng/L with an absolute increase of ≥5 ng/L amongst any postoperative troponins, or ≥65 ng/L, "attributable to a presumed ischemic mechanism (ie, supply-demand mismatch or atherothrombosis) in the absence of an overt precipitating nonischemic cause (eg, pulmonary embolism)". The timestamp for laboratory diagnosis will be set at the time that the sample of elevated troponin was drawn.
    a. Nonischemic causes that may be temporally associated (around the time prior to troponin elevation) were individually chart reviewed, and include PE/DVT, sepsis, rapid atrial fibrillation, cardioversion within 24 hours as per the VISION trial (33). Rapid atrial fibrillation will be established as the presence of atrial fibrillation on ECG with a ventricular rate >100 bpm. Sepsis will be defined as the presence of infection and a systemic inflammatory response (SIRS) and per the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). SIRS requires 2 or more of the following features: core temperature > 38 C or < 36 C; heart rate > 90 beats per minute; respiratory rate > 20 breaths per minute; WBC count > 12 x 109/L or < 4 x 109/L (34).
2. In patients with abnormal baseline troponin values (>14 ng/L) that is considered chronic and stable, postoperative myocardial injury is considered acute if there is postoperatively a ≥20% rise in high-sensitivity cTnT, or an absolute increase in high-sensitivity cTnT of ≥14 ng/L above preoperative values. If a patient was diagnosed as having preoperative acute myocardial infarction, there must be a decrease in preoperative hsTnT to be considered chronic elevation for this rule to apply. Manual physician adjudication will be performed as a double check.

Note that MINS includes myocardial infarction in the AHA definitions. If a patient died before MINS diagnosis within 3 days postoperatively, this will be considered an event - i.e. the outcome is specifically MINS or death, to avoid competing risk bias due to death. However, we anticipate death within 3 days after surgery to be very rare.

Only the first positive MINS event is included, and hemodynamic data will be truncated up to that point. The MINS "diagnosis time" of MINS vs. no MINS is the first troponin in the serial troponin that fits the MINS criteria, with the start time defined as since the start of the surgery.

The exploratory modeling objectives will model both troponin level and MINS definitions.

Vital sign candidate features (predictors)

- Vital signs time series (SBP, MAP, DBP, HR, SpO2): taken from Surginet (intraoperative) and Cerner (preoperatively on the day of surgery, and postoperative)
    - These will be modeled using time series data from 1) intraoperative only, 2) postoperative only, and 3) both intraoperative and postoperative periods, using the following approaches:

- Summary predictor variables as defined by clinicians based on literature (e.g. duration MAP<75, duration HR >100) - different thresholds will be explored
    - **For the primary model, duration MAP<75 will be used (Liem et al.)**
    - Since vitals on the surgical ward may not be measured as frequently, episodes will be defined with the first low value as the start of the event and the first next measurement that is normal as the end of the event.
- Univariate time series (machine learning)
- Multivariate time series (machine learning)

Table 4. Examples of summary variables for vital signs.
These will be modeled based on time stamps as: 1) intraoperative only, 2) postoperative only, and 3) both intraoperative and postoperative periods

Blood pressure	SBP 1. Maximum decrease from preoperative (defined as median past 24h throughout this table) SBP, as a) absolute change (mmHg), and b) relative change (%) 2. Cumulative duration (minutes) 20% below preoperative preoperative SBP 3. Longest single episode (minutes) below a) 80, b) 90, and c)100 mmHg 4. Cumulative duration (minutes) below a) 80, b) 90, and c)100 mmHg MAP 1. Maximum decrease from preoperative MAP, as a) absolute change (mmHg), and b) relative change (%) 2. Cumulative duration (minutes) 20% below preoperative MAP 3. Longest single episode (minutes) below a) 60, b) 65, c) 70, d) 75, e) 80, and f) 85mmHg 4. Cumulative duration (minutes) below a) 50, b) 60, c) 65, d) 70, e) 75, f) 80, and g) 85mmHg

Heart rate	1. Maximum decrease from preoperative heart rate, as a) absolute change (beats per minute, BPM), and b) relative change (%) 2. Maximum increase from preoperative heart rate, as a) absolute change (BPM), and b) relative change (%) 3. Maximum pulse variation (maximum heart rate minus minimum heart rate) 4. Longest single episode (minutes) below 40, 50, or 60, and above 100, 110, or 120 BPM 5. Cumulative duration (minutes) a) below 60, and b) above 100BPM
Oxygen saturation by pulse oximetry: SpO_2	1. Longest single episode (minutes) below a) 88, and b) 90% 2. Cumulative duration (minutes) below a) 88, and b) 90% 3. New postoperative requirement for supplementary oxygen

Other candidate features

For generalizability and to decrease bias, we will select features that are routinely collected. Non-vital sign candidate features include age, sex, urgent/emergent procedure (for the index surgery), postoperative GFR, and comorbidities within the RCRI categories.

***A priori features* in the primary model**

This *a priori* list of predictors will be used for the primary modeling in Objective 1: duration hypotension (summarized as a percentage of duration of MAP<75 mmHg in the duration of time modeled, e.g. postoperative day 0, 1, and 2), age, sex, emergency surgery, RCRI, and postoperative GFR, as well as the postoperative day and the interaction between postoperative day and % duration MAP<75mmHg as detailed below.

Statistical analysis

Missing data

We will exclude patients with no intraoperative or postoperative vital signs and no troponin measurements from the cohort. Complete case analysis will be performed for vital sign features, with each complete case defined as a patient with >=1 vital sign measurement(s) and >=1 troponin measurement(s). Since the frequencies of measurements are different, missing vital signs are not considered missing values for inclusion/exclusion purposes as long as patients meet the complete case criteria. No imputation will be performed for vital sign data.

For features that are not vital signs (e.g. age, sex), we anticipate minimal missing data (as these variables are routinely collected), and assume missing at random. Due to the longitudinal data structure with correlated observations, we opted for a simpler method of imputation for the primary analysis. For features missing <1%, complete case analysis will be

performed; between 1-<10%, multiple imputation; above 10%, the feature would be excluded from the model and the reason for missing data will be investigated.

Data quality
The data quality of the CIHI vs. chart review results of the comorbidity information will be assessed by Pearson correlation, with chart review as the gold standard.

Cohort characteristics
Continuous data will be presented in mean (SD) if normal, and median (IQR) if non-normally distributed. Categorical data will be presented as frequency (%). The following characteristics will be presented as overall group, and stratified by MINS vs. no MINS:

- Age
- Gender
- American Society of Anesthesiologists' physical status classification (ASA)
- Type of anesthesia (general, neuraxial, peripheral, and/or sedation)
- RCRI score and categories: pre-existing TIA/CVA, insulin dependent diabetes, serum creatinine >177 mmol/L, coronary artery disease, congestive heart failure, and high risk surgery including intrathoracic, intraabdominal or suprainguinal vascular surgery
- Charlson Comorbidity Index (CCI) score and categories: history of MI, CHF, PVD, CVA/TIA, dementia, chronic pulmonary disease, connective tissue/rheumatic disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia/paraplegia, moderate to severe CKD, local/metastatic malignancy, AIDS/HIV
- Surgical service
- Duration of surgery
- Surgical priority: emergent/urgent vs. elective
- ICU admission preoperatively
- Cardiovascular medications preoperatively: Angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitor, and beta blockers (based on available names extracted from Cerner; may be missing medications that have been held and not restarted in hospital).
- Estimated blood loss
- Use of intraoperative/postoperative vasopressors/inotropes
  Yes/no (received anything at all)
  Small amount of intraoperative use (phenylephrine (<200 mcg) or ephedrine (<10 mg)
  Significant only (i.e. exclude if small doses of phenylephrine (<200 mcg) or ephedrine (<10 mg)
- Laboratory preoperatively (30 days before surgery): NT-proBNP, hemoglobin, creatinine/GFR, troponin
- Respiratory rate
- Postoperative disposition (ward vs. HAU vs. ICU) - multiple entries possible; time of moving in/out of each unit
- Descriptive statistics of troponin as a continuous variable by postoperative days

- Diagnosis of myocardial infarction, MINS, and postoperative myocardial injury
- MINS troponin monitoring
    - Duration (operative day to the last day of troponin measurement)
    - Numbers of troponin testing done and frequency
    - Time of MINS diagnosis (rule in vs. rule out), hours after end of operation as defined by the event of patient leaves the operating room
- Non-MINS causes of troponin elevation
    - PE/DVT
    - Sepsis
    - Rapid atrial fibrillation
    - Cardioversion < 24 hours
    - Chronic elevation (excluded)
- Vitals monitoring
    - Frequency (plot frequency vs. POD)
    - Duration within POD3
- 30 Day in-hospital mortality

Also, descriptive summaries of the vital statistics as listed in Table 4 will be presented.

Data processing

The Cerner, Surginet, and chart review data will then be linked by de-identified Cerner study ID. The time series time stamps will be shifted to have the start of surgery as 00:00, Jan 1, 2020, in order to standardize the times for longitudinal modeling. Data will then be processed for removal of vital sign artefacts per the Multicentre Perioperative Outcomes Group protocol (35). To generate a final blood pressure dataset, if noninvasive blood pressure and invasive blood pressure are available during the same minute, then the measurement that is 1) not marked as artefact and 2) has a higher systolic blood pressure will be taken. Data will also be processed for calculation of RCRI, determination of the timing of MINS diagnosis, truncation of vital sign time series to the appropriate time stamp (see below), and calculation of duration under threshold of the time series to create vital sign summary variables as described in Table 4 for each postoperative day (0-<24h, 24-<48. 48-<72, and <72-96h after surgery end time). A formal chart review will also be performed to extract data not automatically retrieved from Cerner and Surginet, and verify data quality of automatically extracted comorbidities.

For modeling troponin as a continuous outcome, the vital sign time series will be truncated at the last troponin measurement within 3 days of surgery. For modeling the binary MINS outcome definitions the data will be truncated at the time of troponin laboratory diagnosis of the outcome event, postoperative day 3 (since the MINS protocol monitors for 3 days) or hospital discharge or death, whichever occurs first. All time measurements will be standardized as above in relation to the surgery start time.

Predictive Modeling Approaches
Approach I. Analysis using conventional longitudinal modeling (primary objective)

Data visualization
The initial exploratory analysis of the vital signs and troponin data involves time series visualizations and summaries to explore any potential patterns present in the data that may be associated with troponin quantiles or MINS or myocardial injury diagnosis. Spaghetti plots of the longitudinal data will be created for the outcome and vital signs variables, with lines colour-coded by troponin quantiles or MINS or myocardial injury diagnosis. Other relevant visualizations (scatterplots, boxplots, etc.) examining the associations between the troponin outcome and the vital signs variables will also be created.

Primary Modeling
The primary analysis will involve building a linear mixed effects model (with random intercepts) to predict the maximum daily troponin level between postoperative days 0 to 2 as the continuous outcome. The postoperative days 0, 1, and 2 accounts for approximately 40%, 40%, and 10% of MINS, respectively (4). Due to the limitations in retrospective data and the daily troponin monitoring, we will use day as a unit for time rather than hour to avoid overestimation of precision by readers.

For the primary and secondary models described in Objectives 1 and 2, an *a priori* list of predictors will be used: duration hypotension (summarized as a percentage of duration of MAP<75 mmHg in the duration of time modeled, e.g. postoperative day 1) age, sex, emergency surgery, RCRI, and postoperative GFR, as well as the postoperative day and the interaction between postoperative day and % duration MAP<75 mmHg as detailed below.

For longitudinal modeling, the vital signs data and troponin data will be aggregated to the day level, so that the model can predict at the daily temporal level. If there are multiple troponin measurements on the same day, the maximum will be taken. This aggregation of the data is necessary to account for the fact that the vital signs and troponin measurements are measured at irregular intervals (both across patients and data types), often due to the acting physician's response to the patient's condition. Additionally, due to this characteristic of the raw data, the vital signs predictors will be created such that they are standardized to be robust to the number of daily measurements performed (for example, by taking the percentage of day duration, NOT the total duration, of blood pressure below a specific threshold across all measurements during that day). A categorical time variable (representing the day of the measurement) will be included as a predictor within the model.

Due to the longitudinal nature of the data, we need to include random effects to adjust for the dependence between within-patient daily observations. Thus, at minimum, we intend to include a random intercept corresponding to each patient within the model. However, we may consider including random slopes based on what is observed in the exploratory analysis of the vital signs data, though this would be limited by sample size. Since the effect of a vital signs covariate may be different depending on the day of monitoring, we will investigate interactions between the time predictor and vital signs predictors. This will be performed for only a small number of key time-varying predictors to avoid overfitting, given that the total

number of terms within the model will increase by at least 3 (if the interacting vital signs predictor is continuous or binary) for each additional interaction term included. Visualizations of the effect of each predictor on the response will also be generated, to further investigate their relationships within the context of the model.

To summarize, a simplified example of the primary linear mixed effects model would be: Troponin = intercept + b1BP_day0 + b2day1 + b3day2 + b4BP_day1*day1 + b5BP_day2*day2 + error (plus other non-BP fixed-effect covariates as listed above). An example interpretation would be b1 will correspond to the effect of BP on Day 0, b4 will correspond to the additional effect of BP on Day 1 (with respect to Day 0) and b5 will correspond to the additional effect of BP on Day 2 (with respect to Day 0). However, we will perform exploratory analysis to explore other forms of longitudinal modeling to select the best model based on discrimination and calibration.

Survival analysis will not be employed due to the small variance in the days for the outcome (days 0-2). Also, right censoring is assumed in survival analysis, which does not apply in our case of troponin rise postoperatively as the majority of patients will not have a troponin increase eventually.

Secondary, Sensitivity, and Exploratory Analyses

In addition to the above outlined primary statistical analysis, we intend to conduct additional secondary, sensitivity and exploratory analyses to address Objectives 2 to 4 to examine how well the model performs given the following changes:

- Introduction of transformations or natural cubic splines on continuous predictors or outcomes
- Modelling using a generalized linear mixed effects model for binary definitions of troponin increase (per AHA, as described above).
    - Different truncations of vital sign data stream prior to MINS diagnosis (e.g. no truncation, 12h before diagnosis)
    - If sample size allows: subgroup analysis involving only patients with preoperative troponin; subgroup analysis for patients who are in the intensive care unit perioperatively, as this represents a sicker population.
- Intraoperative only, postoperative only
- Further inclusion of additional predictors (e.g. % duration of HR > 100) from the available vital signs data
- Exploration of the incremental value of vital signs in addition to the RCRI or NT-proBNP in predicting MINS or myocardial injury
- Inclusion of information from postoperative day 3
- Delta troponin (change from preoperative troponin) using linear contrast

Model evaluation

To validate the performance of the linear mixed effects model specified in the primary statistical analysis plan, given the longitudinal nature of the data, a repeated patient-based 5-fold cross-validation will be performed with 100 repetitions (doi: 10.1093/gigascience/gix019). Patient-based record was chosen as record-wise cross validation tends to overestimate prediction accuracy compared to subject-wise cross validation. Note that when using a linear mixed effects model to predict troponin for "new"

patients (such as those in a held-out validation set), there are no unique random effects corresponding to those patients and so we are assuming the mean response for these "new" patients. A "patient-based" approach for the cross-validation approach is performed to avoid data leakage from the training set into the validation set (i.e. a patient's measurements could potentially be present in both the training and validation sets). To quantify predictive performance, the root mean square error (RMSE) will be computed for each repetition, and the corresponding average and standard deviation of those performance measures will be reported. Marginal (i.e. fixed effects only) and conditional (i.e. fixed and random effects) R-squared (Nakagawa and Schielzeth R-squared, doi.org/10.1111/j.2041-210x.2012.00261.x) will be calculated. For assessment of calibration, the predicted values will be averaged across all repetitions (for each actual observation), and a calibration plot will be generated along with measures of the calibration intercept and slope.

For the models involving the binary outcomes of MINS diagnosis, a similar validation approach will be conducted. To assess discrimination, receiver operating characteristic curves (ROCs) will be generated and their area under the curves (AUCs) will be computed for each repetition, forming a distribution of AUCs. Precision-recall curves will also be considered due to the severe class imbalance present in the dataset. Pseudo R-squared will be computed. To assess calibration, the mean predicted class probability will be taken across all repetitions for each observation and then a decile calibration plot will be created, with corresponding calibration intercept and slope.

Decision curve analysis will be done to determine the net benefit of the various binary outcome models across various thresholds, as compared to ordering or not ordering troponin on everyone.

Parameter Count Based on Sample Size and Event Rate

To mitigate potential overfitting of the model onto the available data, we will aim to restrict the number of coefficient terms included within our linear mixed effects model to be at most 15 (i.e. 50 parameters per patient), and 8 variables for the generalized linear mixed effects models (i.e. 10 parameters per outcome event). As there is limited guidance for longitudinal prediction models, this is a choice justified based on a combination of the anticipated sample size, the presence of repeated measures, the modelling of a continuous outcome, the interest in examining interactions between vital signs predictors and the time predictor, and lastly to minimize uncertainty in the predictions.

Approach II. Machine learning exploratory analyses

Aim 1:

We will evaluate several strategies to determine the optimal integration of workflow for imputation and internal bootstrap validation for small medical datasets involving longitudinal data, including modeling vital signs as a time series vs. summary variable. The best performing workflow will be written as a function available on GitHub.

Aim 2:
We will evaluate unsupervised machine learning techniques to describe and cluster patterns of time series data. This would help with classification and prediction, visualization, and interpretability. Then, we will use supervised machine learning techniques to evaluate what patterns in the time series drove predictions in the models, and whether we can determine how much sooner the machine learning models were able to predict myocardial injury events prior to laboratory detection. The visualization codes will be wrapped into a Python package for visualization.

Aim 3:
To determine whether the predictive performance can be improved by using machine learning over traditional models, we will develop and internally validate machine learning models (including boosted trees and neural networks) to predict outcomes as described above, using time series or summary vital sign variables. The modeling is limited by the small sample size and class imbalance, and specific techniques will be explored including temporal-based resampling in the derivation set, one-class learners, and autoencoders.

Participant Confidentiality and Privacy
The dataset contains de-identified perioperative patients. Only those listed on this protocol will have access to the de-identified dataset for the duration of this project. The dataset created for the study will be saved in a password-protected file after the completion of the study or, if applicable, after the publication of study results (whichever happens later). At the end of 5 years, the data will be deleted permanently in accordance to UBC IT policy.

Potential for Risk and/or Harm
This study involves the secondary use of existing de-identified data, and no additional data will be collected. There is no foreseeable risk of the possible disclosure of any identifiable data because the current research will involve de-identified secondary data only.

Report of Findings
The findings from this research will be presented to the St. Paul's Hospital Anesthesia Department through a grand rounds presentation. In addition, there may be the opportunity to present this at an anesthesiology conference and produce a peer-reviewed publication from this data.

Data Dictionary

Source: Surginet extraction

Variable name	**Legend**	**Reason for request**
IDN	ID (deidentified)	To deidentify patients in the dataset
Anesthesia	Principal Anesthesia Technique Epidural General Local Monitored Anesthesia care (MAC) / IV Sedation None Regional Spinal Other Unknown	Cohort characteristics
SBP	Systolic blood pressure with time stamp	Potential predictors: univariate vs. multivariate time series; clinician-defined

		predictor variables.
MAP	Mean arterial blood pressure with time stamp	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
HR	Heart rate/pulse rate with time stamp	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
RR	Respiratory rate with time stamp	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
SpO2	Oxygen saturation by pulse oximetry with time stamp	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
Intraoperative Phenylephrine (>200 mcg)	1/0 Yes/No	Potential predictor Potential confounder
Intraoperative Ephedrine (>10 mg)	1/0 Yes/No	Potential predictor Potential confounder
Intraoperative Norepinephrine	1/0 Yes/No	Potential predictor Potential confounder
Intraoperative Vasopressin	1/0 Yes/No	Potential predictor Potential confounder
Intraoperative Epinephrine	1/0 Yes/No	Potential predictor Potential confounder
Intraoperative Dobutamine	1/0 Yes/No	Potential predictor Potential confounder
Intraoperative Milrinone	1/0 Yes/No	Potential predictor Potential confounder
Time of patient entering room	Time/date	To identify preoperative vitals

Time of patient leaving room	Time/date	To identify postoperative vitals

Source: Cerner extraction (please see appendix for details of the CIHI codes)

Variable name	**Legend/ICD-10 code**	**Reason for request**
IDN	ID (deidentified)	To deidentify patients in the dataset
MRN	ID	Required for manual chart review of variables that cannot be extracted automatically
Age	Age	Cohort characteristics
Gender	Male vs. Female	Cohort characteristics
Surgical priority	E0: STAT E1: <1 hour E2: <4 hours E2OB: <2 hours E3: <8 - 12 hours E4: <48 hours Elective A dichotomized variable of emergent/urgent vs. elective will be created as a predictor in the primary model	Cohort characteristics
Procedure_code	Cerner procedure code	Cohort characteristics
Procedure_text	The corresponding free text to the Cerner procedure code	Cohort characteristics
ASA	American Society of Anesthesia Physical Classification Score Score from 1 - 6 assessed by consulting anesthesiologist	Cohort characteristics

SBP	Systolic blood pressure with time stamp (day of surgery to POD3)	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
MAP	Mean arterial blood pressure with time stamp (day of surgery to POD3)	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
HR	Heart rate/pulse rate with time stamp (day of surgery to POD3)	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
RR	Respiratory rate with time stamp (day of surgery to POD3)	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
SpO2	Oxygen saturation by pulse oximetry with time stamp (day of surgery to POD3)	Potential predictors: univariate vs. multivariate time series; clinician-defined predictor variables.
RCRI	Revised cardiac risk index total score	Potential predictor of MINS
CCI	Charlson comorbidity index total score	Potential predictor of MINS
CVA	Presence of cerebrovascular disease CIHI preoperative diagnoses: G45.x, G46.x, H34.0, I60.x–I69.x 1/0 Yes/No	Potential predictor RCRI, CCI
IHD	Presence of ischemic heart disease CIHI preoperative diagnoses: I20.x, I21.x, I22.x, I24.x, I23.x, I25.x, Z95.1, Z95.5 1/0 Yes/No	Potential predictor RCRI, CCI

CHF	History of congestive heart failure CIHI preoperative diagnoses: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0 1/0 Yes/No	Potential predictor RCRI, CCI
Preoperative creatinine	Value in μmol/L	Potential predictor RCRI
Insulin use	Insulin (medium or long-acting) from medical administrative record 1/0 Yes/No	Potential predictor RCRI
CKD	CKD stage 4-5 or dialysis dependednt CIHI preoperative diagnoses: N18.3, N18.4, N18.5, Z49.0–Z49.2, Z99.2 1/0 Yes/No	Cohort demographics Potential predictor RCRI, CCI
PVD	Presence of peripheral vascular disease CIHI preoperative diagnoses: I70-I79 1/0 Yes/No	Potential predictor of MINS, CCI
Dementia	History of dementia CIHI preoperative diagnoses: F00.x-F03.x, F05.1, G30.x, G31.1 1/0 Yes/No	Potential predictor CCI
Chronic pulmonary disease	History of chronic pulmonary disease CIHI preoperative diagnoses: I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3 1/0	Potential predictor CCI

	Yes/No	
Connective tissue/rheumatic disease	History of connective tissure or rheumatic disease CIHI preoperative diagnoses: M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0 1/0 Yes/No	Potential predictor CCI
Peptic ulcer disease	History of peptic ulcer disease CIHI preoperative diagnoses: K25.x-K28.x 1/0 Yes/No	Potential predictor CCI
Mild liver disease	History of mild liver disease CIHI preoperative diagnoses: B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4 1/0 Yes/No	Potential predictor CCI
Severe liver disease	History of moderate - severe liver disease CIHI preoperative diagnoses: I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7 1/0 Yes/No	Potential predictor CCI
Diabetes uncomplicated	History of diabetes without chronic complications CIHI preoperative diagnoses: E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 1/0	Potential predictor CCI

	Yes/No	
Diabetes complicated	History of diabetes with chronic complications CIHI preoperative diagnoses: E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7 1/0 Yes/No	Potential predictor CCI
Hemiplegia/paraplegia	History of hemiplegia or paraplegia CIHI preoperative diagnoses: G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9 1/0 Yes/No	Potential predictor CCI
Localized malignancy	History of malignancy (including lymphoma and leukemia, except malignant neoplasm of skin) CIHI preoperative diagnoses: C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x 1/0 Yes/No	Potential predictor CCI
Metastatic tumour	History of metastatic solid tumour CIHI preoperative diagnoses: C77.x-C80.x 1/0 Yes/No	Potential predictor CCI
AIDS/HIV	History of acquired immunodeficiency syndrome or human immunodeficiency virus CIHI preoperative diagnoses: B20.x-B22.x, B24.x 1/0	Potential predictor CCI

	Yes/No	
Hypertension	Presence of hypertension CIHI preoperative diagnoses: I10-I15 1/0 Yes/No	Cohort demographics
PE	Presence of pulmonary embolism within MINS window CIHI postoperative diagnoses: I26 1/0 Yes/No	MINS diagnosis criteria
Atrial fibrillation	Presence of atrial fibrillation within MINS window CIHI postoperative diagnoses: I48.x 1/0 Yes/No	MINS diagnosis criteria
Cardioversion	Cardioversion within 24 hours MINS 1/0 Yes/No	MINS diagnosis criteria
Sepsis	Presence of sepsis within MINS window CIHI postoperative diagnoses: R57.2 1/0 Yes/No	MINS diagnosis criteria
MINS	Based on MINS diagnostic criteria as described (primary outcome) 1/0 Yes/No	MINS diagnosis criteria
MIpost	Diagnosis of myocardial infarction postoperatively 1/0 Yes/No	Third Universal Definition or per cardiology note

PMI	Diagnosis of postoperative myocardial injury postoperatively 1/0 Yes/No	StEP criteria
Troponin	Preoperative and postoperative HS troponin values with time stamps Value in ng/L	MINS diagnosis criteria Time of MINS diagnosis Exclusion Criteria Patients who had positive troponin on postoperative day 4 will be excluded, since vital signs are only included up to postoperative day 3 for consistency.
Estimated blood loss	Intraoperative recorded blood loss Volume in mL	Potential predictor
Surgical Service	Vascular General Orthopedics ENT Gynecology Plastics Other	Potential predictor
High risk surgery	Suprainguinal vascular, intrathoracic, intraperitoneal 1/0 Yes/No	Potential predictor RCRI
Disposition postoperatively	Ward vs HAU vs ICU	Cohort Characteristic
HAU admission start time	Time stamp	Determine setting of vital measurement
HAU admission end time	Time stamp	Determine setting of vital measurement
ICU admission start time	Time stamp	Determine setting of vital measurement

ICU admission end time	Time stamp	Determine setting of vital measurement
Preoperative NT-proBNP	Value in ng/L	Potential predictor
Preoperative Hemoglobin	Value in g/L	Cohort characteristics Potential predictor
Preoperative GFR	Value in mL/min	Cohort characteristics Potential predictor
Preoperative beta blocker use	Preoperative use (metoprolol, bisoprolol, carvedilol, atenolol, propranolol, labetalol, nadolol) 1/0 Yes/No	Potential predictor Potential confounder Note that in order to obtain these variables and due to the limited analytic time from the Cerner team, all medications in the patient's medication administration record that is noted as completed were pulled
Preoperative ACEI/ARB	Preoperative use (captopril, enalapril, ramipril, perindopril, lisinopril, candesartan, irbesartan, losartan, telmisartan, valsartan, sacubitril/valsartan) 1/0 Yes/No	Potential predictor Potential confounder Note that in order to obtain these variables and due to the limited analytic time from the Cerner team, all medications in the patient's medication administration record that is noted as completed were pulled
Postoperative Phenylephrine (>200mcg)	1/0 Yes/No	Potential predictor Potential confounder
Postoperative Ephedrine (>10mg)	1/0 Yes/No	Potential predictor Potential confounder

Postoperative Norepinephrine	1/0 Yes/No	Potential predictor Potential confounder
Postoperative Vasopressin	1/0 Yes/No	Potential predictor Potential confounder
Postoperative Epinephrine	1/0 Yes/No	Potential predictor Potential confounder
Postoperative Dobutamine	1/0 Yes/No	Potential predictor Potential confounder
Postoperative Milrinone	1/0 Yes/No	Potential predictor Potential confounder
In hospital mortality	1/0 Yes/No	Outcome Cohort characteristic
Start of surgery (time/date) [Enters OR]	Time/date	To define the start of the time series
End of surgery (time/date) [Leaves OR]	Time/date	To define the start of the postoperative time series
Length of OR	Duration in minutes	Potential predictor
PACU length of stay	Duration in minutes (if available, otherwise calculated based on the following two values)	Potential Predictor
Time of PACU admission	Time/date	For time stamps
Time of PACU discharge	Time/date	For time stamps
Time/date of hospital discharge	Time/date	To verify inclusion criteria
Readmission within 3 days of surgery	1/0 Yes/No	Patients who underwent repeat surgery or were readmitted within the first 72 hours postoperatively will be excluded.
Repeat surgery within 3	1/0	Patients who underwent

days of surgery	Yes/No	repeat surgery or were readmitted within the first 72 hours postoperatively will be excluded.

CIHI – Canadian Institute for Health Information, ICD-10 (International statistical classification of diseases and related problems) codes

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