Study Protocol: Predicting Postoperative Myocardial Injury using Different Definitions of Intraoperative Hypotension

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1. Title of Study

Predicting Postoperative Myocardial Injury: A Retrospective Cohort Study Comparing Absolute versus Relative Definitions of Intraoperative Hypotension.

2. Investigators

- **Principal Investigator:** [Kan Wang]
- **Study Site:** China-Japan Friendship Hospital, Beijing, China

3. Introduction and Background

Postoperative myocardial injury (PMI) is a significant and common complication following non-cardiac surgery, serving as a major contributor to postoperative morbidity and mortality. Intraoperative hypotension (low blood pressure during surgery) is prevalent and mechanistically linked to reduced myocardial perfusion, thereby strongly correlating with PMI. However, a universally accepted definition for intraoperative hypotension remains elusive, leading to inconsistencies in research and clinical practice.

Previous studies have primarily focused on absolute mean arterial pressure (MAP) thresholds, with some retrospective data suggesting an association between MAP < 65 mmHg and increased PMI risk, particularly with longer durations of hypotension. Conversely, recent research has presented conflicting findings, indicating that maintaining higher MAP values (e.g., > 75 mmHg) may not necessarily reduce PMI incidence, and that MAP values ⩾ 60 mmHg may not significantly differ from MAP ⩽ 60 mmHg in terms of all-cause mortality.

Despite the general consensus that insufficient myocardial perfusion due to intraoperative hypotension leads to injury, the optimal definition for "hypotension" in predicting PMI remains controversial. Our preliminary findings suggest a crucial insight: a significant percentage drop from a patient's baseline pre-operative MAP (e.g., > 40% reduction), even if the absolute MAP remains above 60 mmHg, is associated with a

substantially increased risk of PMI. This observation forms the basis of our hypothesis.

This study aims to address this critical gap by comparing the predictive power of absolute MAP thresholds versus the percentage reduction from baseline MAP for postoperative myocardial injury. We anticipate that the relative percentage drop from baseline MAP may offer superior predictive capability for PMI.

4. Research Objectives

- **Primary Objective:** To compare the correlation and predictive strength of baseline MAP percentage decrease versus absolute MAP values with postoperative myocardial injury.
- **Secondary Objectives:**
    - To develop and identify the optimal predictive model for postoperative myocardial injury.
    - To compare the accuracy and performance of different predictive models (e.g., models based on absolute thresholds, relative thresholds, and combined models).

5. Study Design

This is a **retrospective cohort study** utilizing electronic medical records.

- **Study Period:** Data will be collected from January 1, 2020, to December 31, 2025.
- **Study Setting:** China-Japan Friendship Hospital, Beijing, China.
- **Cohort Definition:** All patients meeting the inclusion criteria during the specified time frame will form the study cohort.

6. Study Population

6.1. Inclusion Criteria:

- Patients who underwent elective non-cardiac, non-emergency surgery with general anesthesia at China-Japan Friendship Hospital between 2020 and 2025.
- Surgical duration greater than 1 hour.
- Received at least one cardiac injury marker test (e.g., troponin) within 7 days post-surgery for outcome assessment.
- Patients with American Society of Anesthesiologists (ASA) physical status classification of I to III.

6.2. Exclusion Criteria:

- Patients younger than 12 years old.
- Patients undergoing organ transplant surgery.
- Patients with more than 10 consecutive minutes of invalid or missing intraoperative vital signs data.
- Patients with critical data missingness that prevents reliable analysis (e.g., pre-operative blood pressure data for baseline calculation).

6.3. Sample Size:

The study aims to include approximately 8,000 patients who meet the inclusion criteria from the specified timeframe. Based on previous data, approximately 3,000 patients are expected to experience postoperative cardiac dysfunction (elevated troponin). This large retrospective cohort is anticipated to provide sufficient statistical power for robust analysis and model development.

7. Data Collection

7.1. Data Sources:

Patient data will be extracted retrospectively from the electronic medical records (EMR) system of China-Japan Friendship Hospital. This includes anesthesia records, surgical records, laboratory results, and patient charts.

7.2. Variables to be Collected:

- **Basic Demographics:** Patient ID, name (for record linkage only, then anonymized), sex, age, height, weight, BMI.
- **Past Medical History (Comorbidities):** Hypertension, diabetes mellitus, coronary artery disease (CAD), congestive heart failure (CHF), chronic kidney disease (CKD), cerebrovascular disease, chronic obstructive pulmonary disease (COPD), etc.
- **Pre-operative Data:** Baseline blood pressure, ASA physical status classification, pre-operative blood routine, biochemistry, coagulation function, baseline cardiac injury markers.
- **Surgical Information:** Surgical procedure (classified by ICD-9 into 19 types, e.g., intra-abdominal, orthopedic, neurosurgical), surgical duration (anesthesia start to end time), estimated blood loss, emergency vs. elective surgery.
- **Intraoperative Management:** Types and dosages of anesthetic agents,

vasopressors, inotropes, other relevant medications; intraoperative fluid input and output.

- **Intraoperative Vital Signs:** Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), oxygen saturation (SpO2), end-tidal carbon dioxide (EtCO2). These will be recorded from the anesthesia monitoring system at 15-second intervals.
- **Post-operative Outcomes:** Postoperative cardiac injury marker tests (e.g., troponin levels) within 7 days.
- **Special Intraoperative Events:** Any documented significant events (e.g., massive hemorrhage, cardiac arrest, severe arrhythmias).

7.3. Definition of Key Variables:

- **Baseline Mean Arterial Pressure (MAP):** The stable MAP value recorded from the anesthesia record sheet at the time of anesthesia induction, after patient entry into the operating room.
- **Intraoperative Hypotension (Absolute Thresholds):**
    - Total duration (minutes) of MAP < 45, 55, 65, 75 mmHg.
    - Time-weighted average (TWA) of MAP below these thresholds.
- **Intraoperative Hypotension (Relative Thresholds):**
    - Total duration (minutes) of MAP decrease ⩾ 10%, 20%, 30%, 40%, 50% from baseline MAP.
    - Time-weighted average (TWA) of MAP decrease below these percentage thresholds from baseline.
- **Primary Outcome Measure: Postoperative Myocardial Injury (PMI):**
    - **Description:** PMI is defined as an elevation of cardiac troponin (e.g., high-sensitivity troponin I or T) levels above the 99th percentile upper reference limit (URL) of the local institutional laboratory within 7 days following non-cardiac surgery.
    - **Time Frame:** Within 7 days following non-cardiac surgery.

8. Ethical Considerations

This study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. As a retrospective study utilizing anonymized patient data,

the need for individual patient consent will be reviewed and approved by the Institutional Review Board (IRB) of China-Japan Friendship Hospital prior to data collection. Patient confidentiality will be strictly maintained by de-identifying all data before analysis. Access to raw patient data will be limited to authorized study personnel.

9. Statistical Analysis Plan (SAP)

9.1. Data Management and Preprocessing

- **Data Cleaning:** Data will be checked for completeness, consistency, and accuracy. Any errors will be resolved through standard data cleaning procedures.
- **Outlier Handling:** Outliers in continuous variables will be identified using appropriate statistical methods (e.g., IQR rule) and managed by winsorization, transformation, or through sensitivity analyses to assess their impact on results.
- **Missing Data:**
    - **Assessment:** The extent and pattern of missing data will be quantified. Missingness will be assessed for being missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR).
    - **Imputation:** If data are determined to be MAR, **Multiple Imputation (MI)** using chained equations will be the primary method for handling missing values. Sensitivity analyses will be conducted using different imputation methods or complete-case analysis to assess robustness.

9.2. Descriptive Statistics

- **Objective:** To summarize the demographic, clinical, and intraoperative characteristics of the study population, and the incidence of PMI.
- **Methods:**
    - **Continuous Variables:** Mean ± standard deviation (SD) for normally distributed data, and median with interquartile range (IQR) for non-normally distributed data. Normality will be assessed by visual inspection (histograms, Q-Q plots) and statistical tests (e.g., Shapiro-Wilk test).
    - **Categorical Variables:** Frequencies and percentages.
    - **Hypotension Metrics:** Descriptive statistics (e.g., mean/median duration, TWA) will be presented for each defined absolute and relative hypotension threshold.

9.3. Univariate Analysis

- **Objective:** To identify preliminary associations between patient characteristics, different hypotension metrics, and the occurrence of PMI.
- **Methods:**
    - Comparison of baseline characteristics and hypotension metrics between patients with PMI and those without.
    - **Continuous Variables:** Independent samples t-test (normally distributed) or Mann-Whitney U test (non-normally distributed).
    - **Categorical Variables:** Chi-square test or Fisher's exact test (if expected cell counts are small).
    - P-values and appropriate effect sizes (e.g., mean differences with 95% CIs, odds ratios with 95% CIs) will be reported. A significance level of $p < 0.1$ will be considered for initial screening for multivariable model inclusion.

9.4. Multivariable Logistic Regression Models

- **Objective:** To assess the independent association of absolute and relative MAP thresholds with PMI, adjusting for potential confounders.
- **Methods:**
    - **Model Building Strategy:** Candidate variables will be selected based on univariate analysis results ($p < 0.1$), clinical relevance, and prior literature. To manage multicollinearity and select robust predictors, stepwise selection (forward, backward, or bidirectional) or penalized regression methods like Lasso or Elastic Net will be considered.
    - **Model Specifications for Hypothesis Testing:**
        - **Model A (Absolute Thresholds):** PMI (dependent variable) ~ Primary absolute MAP metrics (e.g., duration of MAP < 65 mmHg, TWA of MAP < 65 mmHg) + selected confounding factors.
        - **Model B (Relative Thresholds):** PMI ~ Primary relative MAP metrics (e.g., duration of MAP decrease $\geqslant$ 40% from baseline, TWA of MAP decrease $\geqslant$ 40% from baseline) + selected confounding factors.

        - **Model C (Combined):** PMI ~ Both primary absolute and relative MAP metrics + selected confounding factors, to assess independent contributions.
    - **Confounding Factors:** Adjusted for age, sex, BMI, relevant comorbidities (e.g., hypertension, diabetes, CAD, CKD), ASA physical status, surgical type, surgical duration, estimated blood loss, and intraoperative vasopressor/inotropic use.
    - **Output:** Adjusted odds ratios (aORs) with 95% CIs and p-values for all predictors.

9.5. Predictive Model Building for Postoperative Myocardial Injury

- **Objective:** To develop and identify the optimal predictive model for PMI.
- **Methods:**
    - **Feature Engineering for Hypotension:** Beyond total duration and TWA, additional features from 15-second interval vital signs may include minimum MAP value, maximum duration of a single hypotensive episode, area under the curve (AUC) of hypotension below specific thresholds (hypotension burden), and MAP variability.
    - **Candidate Models:**
        - **Logistic Regression:** Focusing on the most impactful set of predictors.
        - **Machine Learning Models:** Random Forest, Gradient Boosting Machines (e.g., XGBoost, LightGBM), or Support Vector Machines will be explored to capture complex non-linear relationships and interactions.
    - **Model Selection:** Models will be selected based on performance metrics (AUC, Brier score) from internal validation, and information criteria (AIC/BIC for logistic regression).

9.6. Model Performance Evaluation

- **Objective:** To quantify the predictive ability and reliability of developed models.
- **Methods:**
    - **Discrimination:** Assessed using **Receiver Operating Characteristic (ROC) Curves and Area Under the Curve (AUC)** with 95% CIs.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) will be calculated at various clinically relevant probability thresholds.

- **Calibration:** Assessed by the **Hosmer-Lemeshow Goodness-of-Fit Test** ($p > 0.05$ indicating good fit) and **Calibration Plots** comparing predicted probabilities against observed frequencies.
- **Clinical Utility:** Evaluated using **Decision Curve Analysis (DCA)** to assess the net benefit of using the model across a range of threshold probabilities.

9.7. Comparison of Different Prediction Models

- **Objective:** To directly compare the predictive accuracy of models based on absolute MAP thresholds versus relative MAP thresholds, and other candidate models.
- **Methods:**
  - **AUC Comparison:** Statistical tests like the **DeLong test** will be used to formally compare the AUCs of different models developed on the same dataset.
  - Other performance metrics such as **Brier score**, **Net Reclassification Improvement (NRI)**, and **Integrated Discrimination Improvement (IDI)** will also be compared where appropriate.

9.8. Internal Validation

- **Objective:** To assess the stability and generalizability of the final predictive model and to correct for optimism in performance estimates.
- **Methods:**
  - **K-fold Cross-Validation:** The dataset will be randomly split into K folds (e.g., 5-fold or 10-fold). The model will be trained on K-1 folds and tested on the remaining fold, repeated K times. Average performance metrics across iterations will provide a robust estimate.
  - **Bootstrap Resampling:** Repeatedly drawing samples with replacement (e.g., 500-1000 times) from the original dataset. Models will be trained on bootstrap samples, and performance assessed on both the bootstrap samples and the original dataset to derive bias-corrected estimates.

9.9. Statistical Software

All statistical analyses will be performed using appropriate statistical software packages such as R (e.g., tidyverse, glm, pROC, rms, caret, mice, glmnet packages) or Python (e.g., pandas, numpy, scikit-learn, statsmodels libraries).

9.10. Significance Level

A two-sided p-value of less than 0.05 will be considered statistically significant for all analyses, unless otherwise specified (e.g., for variable screening in univariate analysis).
