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Prediction of postoperative myocardial injury in patients undergoing laparoscopic pheochromocytoma/paraganglioma resection: protocol for an ambispective cohort study

Ling Lan ,[1,2] Ye Ma,[1] Yifei Zhao,[1] Yaohan Li,[1] Yi Zhang,[1] Le Shen ,[1,2] Yuelun Zhang ,[3] Yuguang Huang[1,2]

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[1]Department of Anesthesiology, Peking Union Medical College Hospital, Beijing, China
[2]State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Beijing, China
[3]Medical Research Center, Peking Union Medical College Hospital, Beijing, China

Correspondence to
Professor Le Shen;
pumchshenle@163.com

ABSTRACT

Introduction Pheochromocytoma/paraganglioma (PPGL) resection remains a high-risk surgical procedure owing to severe haemodynamic instability, which can lead to myocardial injury after non-cardiac surgery (MINS). MINS is the most common and easily overlooked cardiovascular complication and results in increased postoperative mortality and prolonged inpatient hospitalisation. We aimed to develop and validate a predictive model for MINS in patients undergoing laparoscopic PPGL resection.

Methods and analysis The PPGL-MINS study is a single-centre, observational, ambispective cohort study that includes patients undergoing elective laparoscopic PPGL resection under general anaesthesia at the Peking Union Medical College Hospital (PUMCH) between 1 January 2013 and 31 May 2025. We expect to enrol 700 patients, including at least 550 patients retrospectively and 150 patients prospectively. A prediction model will be developed for the retrospective cohort (training cohort) of patients from 1 January 2013 to 31 December 2022. Possible clinically relevant variables, particularly intraoperative blood pressure and heart rate, will be selected as candidate predictors. Stepwise and least absolute shrinkage and selection operator regression will be used for predictor selection. Multivariate logistic regression will be used to develop the prediction model, which will be presented as a nomogram. The developed model will be used to assess discrimination with the receiver operating characteristic curve and area under the curve value, calibration with the Hosmer-Lemeshow test and calibration curve, and clinical usefulness with decision curve analysis. Internal validation will be assessed with bootstrap. For external validation, we will use an independent prospective cohort (validation cohort) of patients from 1 March 2023 to 31 May 2025.

Ethics and dissemination The study protocol has been approved by the Research Ethics Committee of PUMCH (IRB-K2893). Written informed consent will be obtained from all participants in the prospective cohort before enrolment in the study. We aim to publish and disseminate the findings in peer-reviewed journals and at scientific conferences.

Trial registration number NCT05752773.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A bidirectional cohort study is preferred to develop and validate predictive models for single-centre rare disease analyses.
⇒ Least absolute shrinkage and selection operator regression is used for data dimension reduction and predictor selection, in addition to stepwise regression.
⇒ In addition to preoperative factors, this study includes intraoperative haemodynamic parameters (blood pressure and heart rate) as candidate predictors of myocardial injury.
⇒ The external applicability of clinical prediction models developed from single-centre data may be limited.

INTRODUCTION

Pheochromocytoma and paraganglioma (PPGL) are rare catecholamine-secreting tumours arising from chromaffin cells in the adrenal medulla and sympathetic ganglia, with an overall incidence of 0.18–0.66 per 100 000 person-years in the general population.[1–3] PPGL resection, as the cornerstone treatment, remains a high-risk surgical procedure owing to severe intraoperative haemodynamic instability[4] despite utilisation of laparoscopy[5] and preoperative medical treatment,[6 7] which may lead to cardiovascular complications.

Cardiovascular complications are the leading cause of death within 30 days of non-cardiac surgery.[8 9] Myocardial injury after non-cardiac surgery (MINS), defined as troponin elevation exceeding the 99th percentile of the reference value owing to ischaemia, with or without accompanying symptoms or signs,[10] is increasingly being recognised as the most common cardiovascular complication.[11] Its incidence is 8%–20%,[10 12 13] and >80%

of patients present with no symptoms or have clinically 'silent' symptoms.[14 15] Asymptomatic MINS is also associated with increased 30-day and 1-year mortality.[16] Several international guidelines[13 17 18] recommend early detection and multidisciplinary management of asymptomatic MINS in high-risk patients undergoing high-risk surgical procedures. Our previous single-centre study[19] retrospectively investigated the incidence of MINS after laparoscopic resection of pheochromocytomas in a Chinese population and found it to be 12%. In addition, surgeons frequently overlook asymptomatic patients with MINS, potentially contributing to increased long-term mortality.

Preventing cardiovascular complications requires thorough cardiac risk assessment using validated risk calculators.[9 20] However, current preoperative risk stratification tools exhibit variability in input variables, population derivation and outcome definitions.[20] Commonly used preoperative cardiac risk calculators, such as the Revised Cardiac Risk Index and the American College of Surgeons National Surgical Quality Improvement Program, demonstrate suboptimal predictive performance for MINS.[21 22] However, these tools failed to adequately predict the risk of postoperative troponin elevation and all-cause mortality after 1 year.[23 24] Moreover, several intraoperative cardiac risk factors (eg, hypotension,[25–28] tachycardia,[29 30] hypoxaemia[31 32] and bleeding[33 34]) are not integrated into these risk calculators, thereby diminishing their predictive accuracy. Thus, we established a study protocol to develop and validate a perioperative predictive model for MINS after laparoscopic PPGL resection.

METHODS AND ANALYSIS

Study design and setting

This single-centre, observational, ambispective cohort study is to be conducted at Peking Union Medical College Hospital (PUMCH), Beijing, China. Patients undergoing elective laparoscopic PPGL resection between 1 January 2013 and 31 December 2022 and between 1 March 2023 and 31 May 2025 will be selected as the training (retrospective cohort) and validation (prospective cohort) cohorts, respectively. A prediction model for MINS will be developed and internally validated based on data from a retrospective training cohort. External validation of the model will be based on data from an independent prospective validation cohort. We completed our study design on 22 December 2022, and final approval from the Research Ethics Commission of PUMCH was obtained on 7 January 2023 (approval number: IRB-K2893). Written informed consent will be required in the prospective cohort; however, this requirement is waived for the retrospective cohort due to the retrospective nature of the data collection.

Study population and eligibility criteria

Adult patients who underwent elective laparoscopic PPGL resection under general anaesthesia at PUMCH will be included in this study. Patients undergoing open or laparoscopic conversion to open PPGL resection; patients with cardiac paraganglioma, carotid body tumour or jugular tympanic paraganglioma; patients with anaemia (haemoglobin level below 120 g/L) before surgery; and patients with preoperative elevated troponin I level (the 99th percentile upper reference limit is 56 ng/L) or history of cardiac surgery will be excluded from the study. PPGL will be diagnosed based on postoperative pathological results, tumour location and endocrine function, as evaluated using preoperative diagnostic imaging (abdominal CT or metaiodobenzylguanidine scintigraphy) and endocrine tests (24-hour urinary catecholamine level or plasma metanephrine and normetanephrine levels). Patients in the prospective cohort will be tested for high-sensitivity cardiac troponin I levels (Atellica Immunoassay Analyzer, Siemens Healthineers) in the first 3 days after surgery and will be followed up for adverse cardiovascular events during the hospital stay.

Sample size

The sample size required to develop the MINS prediction model is estimated as follows: The occurrence of MINS is a dichotomous statistical event, and the number of outcome events (MINS) could be conservatively estimated according to the '10EPV' rule, that is, each predictor included in the model needed at least 10 positive events (10 events per variable (10EPV)) to estimate the outcome. Based on the simplicity rule of the prediction model, we expected to include five to eight predictors in the final model and calculated the required number of positive outcome events to be at least 80. Our previous retrospective study showed an incidence of MINS of 12% during laparoscopic pheochromocytoma resection. Therefore, the sample size was estimated to be at least 666. Considering missing data or subjects who withdraw from the study, we expected to enrol 700 patients, including at least 550 patients retrospectively and 150 patients prospectively.

Outcome definition

The predicted outcome was MINS occurring within 3 days of surgery. MINS was defined as an elevated troponin I level exceeding the 99th percentile upper reference limit owing to cardiac ischaemic causes, according to the VISION investigators.[10 13] For patients with elevated troponin I levels, the study personnel will search for evidence of ischaemic symptoms, ECG changes and a diagnosis of myocardial infarction.

Candidate predictors and data collection

Possible clinically relevant variables following a review of the literature and consensus opinion by an expert group during the perioperative period in this ambispective cohort will be selected as candidate predictors of MINS to minimise selection bias. Training data set collection will be performed in the respective cohort through a retrospective review of the hospital electronic medical records and anaesthesia information system. The validation data

set derived from the prospective cohort will be collected using standard case report forms to reduce recall bias and provide more accurate data collection. Preoperative, intraoperative and postoperative data will be collected from each patient.

Preoperative variables include age, sex, body mass index, American Society of Anesthesiologists physical status, smoking history, alcohol use, diabetes mellitus, hypertension, previous ischaemic heart disease or stroke, previous congestive heart failure, haemoglobin level, troponin I level, creatinine level, 24-hour urinary catecholamine level, tumour size and location, preoperative medical treatment, and non-invasive blood pressure (BP) and heart rate (HR) before surgery. Ischaemic heart disease refers to a history of myocardial infarction, positive exercise test result, current complaint of chest pain, or nitrate use or ECG with pathological Q waves; it also includes a history of coronary bypass surgery or angioplasty. Stroke refers to ischaemic stroke (thrombotic/embolic/systemic hypoperfusion) or haemorrhagic stroke (intracerebral or subarachnoid haemorrhage).

Intraoperative variables include haemodynamic parameters (HR, invasive systolic BP, diastolic BP and mean arterial pressure) per 10–20 s, the type and dose of vasoactive agents used, lactic acid level in arterial blood, pneumoperitoneum pressure during tumour dissection, surgical duration, crystalloid and colloid volumes, estimated blood loss, red blood cell count and fresh frozen plasma transfusion.

Postoperative variables include prolonged hypotension needing vasopressor support, haemoglobin and troponin I levels in the first 3 days after surgery, in-hospital cardiovascular complications and mortality.

Data analysis and predictor selection

Intraoperative haemodynamic instability is defined as intraoperative hypertension, hypotension, tachycardia and a combination of these.

- Intraoperative hypertension: Intraoperative hypertension is defined as three consecutive data points (≥30 s) of which systolic BP is greater than or equal to the threshold (level 1: 160 mm Hg; level 2: 170 mm Hg; level 3: 180 mm Hg; level 4: 190 mm Hg; level 5: 200 mm Hg).
- Intraoperative hypotension: Intraoperative hypotension is defined as three consecutive data points (≥30 s) of which the mean arterial pressure is less than or equal to the threshold (level 1: 65 mm Hg; level 2: 60 mm Hg; level 3: 55 mm Hg; level 4: 50 mm Hg; level 5: 45 mm Hg).
- Intraoperative tachycardia: Intraoperative tachycardia is defined as three consecutive data points (≥30 s) of which HR is greater than or equal to the threshold (level 1: 100 beats per minute (bpm); level 2: 110 bpm; level 3: 120 bpm; level 4: 130 bpm; level 5: 140 bpm).
- Intraoperative hypertension with tachycardia: Intraoperative hypertension with tachycardia is defined as the combination of intraoperative hypertension and tachycardia.
- Intraoperative hypotension with tachycardia: Intraoperative hypotension with tachycardia is defined as the combination of intraoperative hypotension and tachycardia.

To ensure data reliability, we will exclude patients with missing information on more than three of the candidate predictors, use appropriate imputation techniques to handle missing information on three or fewer candidate predictors and conduct sensitivity analyses to assess the robustness of the results. The selection process for predictive factors will adhere to the following principles: First, the variance inflation factor (VIF) will be calculated between clinically sensitive associations within all candidate variables to limit collinearity and ensure a parsimonious model. Variables with a VIF >10 will be removed from the data analysis.[35] Second, stepwise and least absolute shrinkage and selection operator (LASSO) regression will be used for predictor selection. Forward selection, backward elimination and a combined approach called bidirectional elimination will be applied in stepwise regression for predictor selection, in which the Akaike information criterion is used as the stopping rule.[36] LASSO regression with penalty tuning parameter (λ) selection using 10-fold cross-validation via minimum criteria will also be used for predictor selection.[37] Finally, we will compare differences in predictor selection results between the two methods .

Model development and validation

Multivariate logistic regression will be applied for model development using the selected predictors in the training data set. Discrimination will be evaluated using the receiver operating characteristic curve and area under the curve.[37] Calibration will be assessed using the Hosmer-Lemeshow test and calibration curve.[38] Clinical usefulness will be evaluated using decision curve analysis.[39] Bootstrapping will be used to validate the model internally. External validation will be implemented in the prospective cohort (temporal validation).

Patient and public involvement

None.

ETHICS AND DISSEMINATION

The study protocol has been approved by the Research Ethics Committee of PUMCH (IRB-K2893) and the study is registered at ClinicalTrials.gov (NCT05752773). Every participant in the prospective validation cohort will receive detailed information about the study from the research personnel and will be asked to sign an informed consent form before participating. Participants will have the right to withdraw from the study at any time, and researchers could discontinue the study (eg, in the case of severe adverse events). The ethics committee will supervise the study to track any amendments or serious adverse events and has the right to terminate the study. Any modifications to the study protocol will require agreement from all authors (LL, YFZ, YL, YZ, YLZ, LS and

YH) and will be updated in the trial registry (ClinicalTrials.gov). The results will be submitted for publication in an international peer-reviewed journal.

Contributors LL, LS and YH conceived and designed the study. LL drafted the manuscript with input from YM, YFZ, YL and YZ. LL and YLZ contributed to study design and methodology. All authors revised and approved the final version of the manuscript. LS is the guarantor.

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Competing interests None declared.

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ORCID iDs
Ling Lan http://orcid.org/0000-0002-9215-5231
Le Shen http://orcid.org/0000-0002-2563-0012
Yuelun Zhang http://orcid.org/0000-0001-7990-9003

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