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Protocol for the derivation and external validation of a 30-day postoperative pulmonary complications (PPCs) risk prediction model for elderly patients undergoing thoracic surgery: a cohort study in southern China

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ABSTRACT

Introduction Postoperative pulmonary complications (PPCs) occur after up to 60% of non-cardiac thoracic surgery (NCTS), especially for multimorbid elderly patients. Nevertheless, current risk prediction models for PPCs have major limitations regarding derivation and validation, and do not account for the specific risks of NCTS patients. Well-founded and externally validated models specific to elderly NCTS patients are warranted to inform consent and treatment decisions.

Methods and analysis We will develop, internally and externally validate a multivariable risk model to predict 30-day PPCs in elderly NCTS patients. Our cohort will be generated in three study sites in southern China with a target population of approximately 1400 between October 2021 and December 2023. Candidate predictors have been selected based on published data, clinical expertise and epidemiological knowledge. Our model will be derived using the combination of multivariable logistic regression and bootstrapping technique to lessen predictors. The final model will be internally validated using bootstrapping validation technique and externally validated using data from different study sites. A parsimonious risk score will then be developed on the basis of beta estimates derived from the logistic model. Model performance will be evaluated using area under the receiver operating characteristic curve, max-rescaled Brier score and calibration slope. In exploratory analysis, we will also assess the net benefit of Probability of PPCs Associated with THoracic surgery in elderly patients score in the complete cohort using decision curve analysis.

Ethics and dissemination Ethical approval has been obtained from the Institutional Review Board of the Affiliated Cancer Hospital and Institute of Guangzhou Medical University, the Second Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine and the University of Hongkong—Shenzhen Hospital, respectively. The final risk prediction model will be published in an appropriate journal and further disseminated as an online calculator or nomogram for clinical application. Approved and anonymised data will be shared.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ In this prospective, multicentre, cohort study, we will derive and validate, for the first time, the risk prediction model of postoperative pulmonary complications (PPCs) in elderly patients undergoing non-cardiac thoracic surgery.
⇒ We regard prolonged oxygen supplement as an independent PPC, based on local standardised care pathways after thoracic surgery, in order to facilitate early detection of patients at risk of occult hypoxaemia.
⇒ The model will be validated internally (to quantify model optimism) and externally (to evaluate whether it can remain accurate in different scenarios and future uses).
⇒ The participating centres are from southern China only, which may cause a selection bias.
⇒ In spite of the non-random splitting of data into development and validation cohort, we are still not able to assert the model's performance in the external validation cohort as its sample size is relatively small. Suitability for extrapolation entails a large external validation.

Trial registration number ChiCTR2100051170.

INTRODUCTION

Postoperative pulmonary complications (PPCs) remain the leading cause of morbidity after non-cardiac thoracic surgery (NCTS), relating to prolonged length of stay (LOS), increased healthcare costs, mortality and even cancer recurrence.[1–5] The high incidence of PPCs in elderly NCTS patients, up to 60%, is mainly due to the injury of anatomical structures respiratory function (ie, resection of the lung parenchyma, diaphragmatic dysfunction), the smoking-related respiratory

morbidity (chronic obstructive pulmonary disease (COPD), cancer) and the frailty combined with ageing (decline in physiological reserves). These indispensable predisposing factors of PPCs are compounded by the adverse effects of one lung ventilation (OLV) on postoperative pulmonary function.[2 6–9]

Consequently, assisting elderly patients and families in making decisions congruent with their values and prognostic goals is a critical consideration.

Predictive models have been applied to identify patients at risk for postoperative complications by healthcare providers and policymakers, so as to formulate individualised preventive algorithms and allocate healthcare resource efficiently.[10] Moreover, the selected methodology must be stringent and comply with the guidelines of good clinical practice to make the model accurate and generalisable. A systematic review identified 21 prediction models for PPC, however, none of them completely abided by the recommended steps for the model derivation and validation.[11] Furthermore, current prediction models referring to NCTS patients are scarce, and hence the models dedicated to elderly NCTS patients are more negligible.[12]

Current prediction models that are not applicable to NCTS patients are driven primarily by procedure type, sample size, outcome definition and methodology. The 'Assess Respiratory Risk In Surgical Patients In Catalonia' (ARISCAT) risk score is a highly regarded model that retained sufficient predictive power in a large external validation cohort, but it is not specific to NCTS patients.[13] The plausibility that ARISCAT score is not suitable for NCTS patients is enhanced by the following limitations. First, the development cohort of this study simply consisted of 35 NCTS patients, accounting for 1.4% of sample size, and thus reduced the specificity of ARISCAT score. Furthermore, the PERISCOPE study (an external validation cohort of ARISCAT score) also involved small sample size of NCTS patients.[14] Second, the ARISCAT risk score is a preoperative score unable to take intraoperative variables into consideration. While intraoperative events, such as fluid administration (type and amount), ventilation setting (even within protective limits), desaturation and use of vasoactive agents, are major precipitating factors for development of PPCs, incorporation of these variables could thus strengthen predictability.[15–19] Third, neoadjuvant chemotherapy can reduce the tumour burden and improve resection rate, but whether the immunosuppressive effect of neoadjuvant chemotherapy can promote the development of PPCs is also a consideration in clinical practice.[20] The 'Local Assessment of Ventilatory Management During General Anaesthesia for Surgery' (LAS VEGAS) score composed of 13 perioperative variables demonstrated moderate predictive performance, though it outperformed ARISCAT risk score in the full cohort analysis, probably due to geographic distributions and the addition of intraoperative events. Notably, LAS VEGAS score is also narrowed by the exclusion of cardiothoracic surgery patients, the absence of external validation, and the majority of lower risk patients.[21] Importantly, a recent study suggested that ARISCAT and LAS VEGAS score could overestimate the risk of developing PPCs.[22] The 'Surgical Lung Injury Prediction' (SLIP) and refined SLIP-2 model are two prediction models specialised on a single adverse outcome, acute lung injury/acute respiratory distress syndrome (ALI/ARDS), merely based on preoperative characteristics and procedure-related factors. They also have limitations as a consequence of poor performance in external validation cohorts, thereby precluding their generalisability.[23 24] The 'Melbourne Risk Prediction Tool' showed a poor performance in an external validation, with less than one third of patients being discriminated correctly, so the tool should be used with caution.[25] Though the 'thoracic surgery scoring system' (Thoracoscore) using 15 000 patients data exhibited good internal and external validity, it is derived to predict 30-day mortality in thoracic surgery.[26] While other available predictive tools, such as such as the 'Predictors of Respiratory Insufficiency and Mortality (PRIM)' and the 'Score for Prediction of Postoperative Respiratory Complications', signified a good discriminative ability, they were unable to predict a composite of PPCs, as the primary outcome they focused on was the need for postoperative mechanical ventilation.[27 28] Accordingly, there is no 'one-size-fits all' model regarding risk identification and stratification. In addition, the performance of these models can fade over time for reasons including changes in the demographics, such as an ageing population and frailty status, changes in the type of surgery, such as more minimal invasive technique and complicated procedure, and improvements in perioperative management, such as prehabilitation, goal-oriented haemodynamic therapy and preventive ventilation strategy.[29–31]

To this end, the development of an accurate PPCs prediction model specific to elderly NCTS patients is warranted. Therefore, we will deploy adequate statistical processing and standardised reporting on performance in terms of accuracy, reliability and practicality. These steps include: (1) variable selection based on published data, clinical expertise, pathophysiological reasoning and practical considerations in future clinical use; (2) bootstrapping technique after multivariable logistic regression to lessen predictors, and further to avoid overfitting and estimate the stability of development cohort dataset; (3) robust internal validation via bootstrapping to avoid overoptimistic results as with classical method; (4) external validation to facilitate extrapolation; (5) a simplified risk score and derived three stratums to optimise readiness and (6) assessment of the net benefit of Probability of PPCs Associated with THoracic surgery in elderly patients (PATH) score and ARISCAT score in the complete cohort using decision curve analysis (DCA). We suppose that PATH score will not only be a robust, generalisable and pragmatic model for early identification of elderly patients at risk for PPCs, but also a tool to facilitate shared decision-making to determine the appropriate level of care following the procedure.

METHODS

Study setting and design

This prospective, multicentre, observational study will be performed at three sites within Guangdong, China, between October 2021 and December 2023. The Affiliated Cancer Hospital and Institute of Guangzhou Medical University (Guangzhou, Guangdong, China with principal investigator (PI), YY) will serve as the coordinating centre. Additional study sites will be the following: The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangzhou, Guangdong, China with co-PI, Haiyan Wang) and The University of Hongkong—Shenzhen Hospital (Shenzhen, Guangdong, China with co-PI, TJ). The Affiliated Cancer Hospital and Institute of Guangzhou Medical University is responsible for development and maintenance of the case report forms (CRF), data management and analysis. Results will be reported in accordance with the standard of Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement.[32] The current study protocol is the fourth version.

Study population

Participant recruitment

Inclusion criteria

1. Aged 65 or greater.
2. Both genders.
3. American Society of Anaesthesiologists (ASA) physical status classification I–IV.
4. Diagnosed with pulmonary, oesophageal or mediastinal disorders.
5. Undergoing elective open or video-assisted thoracic surgery (VATS), including wedge resection, segmentectomy, sleeve lobectomy, lobectomy, pneumonectomy, oesophagectomy or resection of the mediastinal tumour.
6. General anaesthesia with OLV or bronchial blocker.
7. Voluntary participation in the trial and signed informed consent.

Exclusion criteria

1. Patients who deny permission to use their health information for research.
2. Patients who are reoperated due to postoperative complications during the 30-day follow-up.
3. Patients with preoperative tracheal intubation or tracheotomy.
4. Patients scheduled to be admitted to Intensive Care Unit (ICU) postoperatively.
5. Life expectancy of less than 30 days due to extensive tumour metastasis.

Study plan

Eligible study patients will be prospectively identified from the daily surgical schedule at three institutions (October 2021–December 2023). All patients scheduled for thoracic surgery will be screened 1 day before the operation for eligibility at the preoperative evaluation clinic (or on Friday for those who will undergo surgery the following Monday). Eligible patients will be informed by the study team coordinator. For the sake of voluntary participation, all patients will be informed about the aims, procedures and benefits. If interested in enrolment, the patients or their next of kin will sign the written consent form in triplicate. Reasons for leaving the study are either the withdrawal of the patient's consent or the cancellation of the planned surgery as well as violations of the study protocol. Patients who don't receive any follow-up after discharge are excluded from the statistical analysis, unless they have suffered from PPCs before discharge. Integrality of the preoperative dataset is attempted, but sporadically missing data are not a stringent exclusion criterion. A 90-day follow-up after surgery is also not mandatory for the evaluation of predictors of PPCs. The participants' timeline from screening to follow-up is shown in table 1.

Data collection

The study team consists of a data safety and management board (DSMB) and local investigators who are all anaesthesiologists. The DSMB includes three senior anaesthesiologists from individual study sites, one surgeon and one biostatistician. The DSMB will provide independent oversight of the PATH study and will review the study data for the participant safety as well as CRF storage. To assess the quality of data collection and recruitment, DSMB will

Table 1 PATH study participants' timeline

Examinations	Screen	Inclusion	Visit 0 1 day before surgery	Surgery	Visit 1 30 day after surgery	Visit 2 30 day after surgery	Visit 3 90 day after surgery
Inclusion criteria	X						
Exclusion criteria	X						
Informed consent		X					
Data collection			X	X			
PPCs					X		
Mortality						X	X

PATH, Probability of PPCs Associated with THoracic surgery in elderly patients; PPCs, postoperative pulmonary complications.

also audit the medical records of a random sample of 70 patients (5% of the sample) from three centres. In each centre, the number of patients audited is proportional to the number of patients recruited. The data will be entered into the Epidata V.4.6 database protected by password only accessible to investigators. Then, the data will be exported from Epidata database to a statistical package for analysis by biostatisticians independent of the study.

Predictor variables

Candidate PPCs predictors are selected according to the investigators' consensus on measurable and clinically meaningful preoperative and intraoperative variables, which are based on published data, clinical expertise, pathophysiological reasoning and practical considerations for future implementation in clinical practice. These data are collected prospectively from the medical record and patient anamnesis by independent investigators who are blinded to the evaluation of endpoints.

Preoperative potential predictors

1. Patient demographic data including age (years), gender, height (cm), weight (kg) and body mass index (kg/m^2).
2. ASA PS classification, functional status, forced expiratory volume in the first second % predicted (FEV1%), forced vital capacity % predicted (FVC%), the ratio FEV1/FVC and respiratory infection in the last 30 days.
3. Smoking status (former smoker, current smoker or never smoker) and alcohol intake.
4. Oxyhaemoglobin saturation by pulse oximetry in air, preoperative anaemia and preoperative hypoalbuminaemia.
5. Chronic comorbidities including disseminated cancer, diabetes mellitus, hypertension, coronary artery disease, COPD, asthma, chronic heart failure, obstructive sleep apnoea syndrome, gastro-oesophageal reflux disease, chronic kidney or liver dysfunction, or other respiratory diseases (such as bronchiectasis, pneumoconiosis or pulmonary fibrosis).
6. Neoadjuvant chemotherapy.

Intraoperative potential predictors

1. Type of surgery (open or VATS), procedure (wedge resection, segmentectomy, sleeve lobectomy, lobectomy, pneumonectomy, oesophagectomy or resection of the mediastinal tumour), duration of surgery (min), duration of anaesthesia (min), duration of OLV (min).
2. Ventilation mode (volume control, pressure control, pressure-regulated volume control or others).
3. Tidal volumes (mL/kg predicted body weight [PBW]), respiratory rate (bpm), positive end-expiratory pressure (PEEP) (cmH_2O), P_{peak} (cmH_2O), P_{plat} (cmH_2O), Cdyn (ml/cmH_2O), driving pressure (cmH_2O), recruitment manoeuvres pressure (cmH_2O) and fractional inspired oxygen (FiO_2).
4. Fluid infused (mL/kg PBW), blood transfusion.
5. Type of anaesthesia (totally intravenous, volatile or balanced).
6. Episodes of desaturation, hypotension or arrhythmia.
7. Vasoactive drugs support, reversal of neuromuscular block agents (NMBA)s.

CRF and definitions of predictive variables are shown in online supplemental digital content 1 and 2.

Outcomes and definitions

Primary outcomes

The primary outcome will be the incidence of PPCs within the first 30 postoperative days (POD30). This outcome will be a composite encompassing unplanned supplementary oxygen, atelectasis, respiratory failure, ARDS, pneumonia, pleural effusion, pneumothorax, bronchospasm, aspiration pneumonitis, unplanned new or prolonged invasive mechanical ventilation, as European Perioperative Clinical Outcome defined. Patients with PPCs will be identified prospectively by consulting medical records in real time to find events that fulfil any PPCs definition, including clinical diagnoses (pneumonia, bronchospasm and/or ARDS), radiological diagnoses (presence of any degree or location of atelectasis, pneumothorax and/or pleural effusion), and therapies for respiratory insufficiency (prolonged supplemental oxygen by nasal cannula (NC) or face mask (FM), and/or unplanned new or prolonged invasive mechanical ventilation). Definitions of PPCs are detailed in table 2.[3 21] The investigators will also make a telephone call on POD30 to review whether a PPC is present after the surgery till now and record the symptoms, severity and type of PPCs in detail on the CRFs.

The secondary outcomes will be postoperative LOS, and 30-day and 90-day mortality.

Sample size

Our sample size was based on inclusion of all eligible elderly patients undergoing thoracic procedures between October 2021 and December 2023 at three study sites simultaneously. We assumed that this sample size would be adequately powered to derive our development model. Based on previous literature and a retrospective study in our centre, an anticipated incidence of 30-day PPCs was approximately 40% in a mixed cohort of elderly patients undergoing thoracic procedures.[4 8–10] Assumption of a required number of 10 events per variable to be estimated by a logistic regression model, the size of development cohort will be determined to be at least 1000 patients. In order to obtain a reasonable number of events for the separate external validation cohort, the planned sample size will be set to at least 1400 patients. The development subsample (approximately 70% of total patients) will be used to construct model in the coordinating centre site and the validation subsample (approximately 30% of total patients) to validate the model's performance of discrimination and calibration in other two centre sites.

Table 2 Definitions of postoperative pulmonary complications

Complications	Definitions
Prolonged oxygen supplement	Supplemental oxygen administered by NC or FM due to PaO_2<60 mm Hg, a ratio of PaO_2 to inspired oxygen fraction <300, or SpO_2 ≤92% on atmospheric air, excluding oxygen supplementation given as standard care (eg, 6 hours after postanesthesia care unit (PACU) discharge for wedge resection, 24 hours for segmentectomy, 48 hours for (sleeve) lobectomy, 72 hours for pneumonectomy and esophagectomy based on our local standard postoperative management pathway)*
Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm towards the affected area and compensatory overinflation in the adjacent non-atelectatic lung
Respiratory failure	PaO_2<60 mm Hg, a ratio of PaO_2 to inspired oxygen fraction <300 or SpO_2<90% despite oxygen administration by NC or FM, or need for non-invasive positive ventilation
ARDS	According to the Berlin definition[33]
Pneumonia	Presence of a new or progressive radiographic infiltrate plus at least two of three clinical features; fever >38°C, leucocytosis or leucopenia (WCC count >12 x10^9/L or <4x10^9/L) or purulent secretions
Pleural effusion	Chest X-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura on the chest X-ray
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents
Unplanned new or prolonged invasive mechanical ventilation	After discharge from operating room

*Presupposed a preoperative oxygen saturation >92%.
ARDS, acute respiratory distress syndrome; FC, face mask; NC, nasal cannula; WCC, white cell count.

Missing data

Outcome data will be complete for all participants. Missing predictor data will be processed using complete case analysis where ≤5% of the values for a given predictor are missing, while >5% will be multiply imputed. Frequencies of missing values will be reported for all potential predictors and the outcomes.

Statistical methods

Kolmogorov-Smirnov test will be used to evaluate the normal distribution of continuous variables. For the description of the cohorts, normally distributed continuous data will be presented as means±SD, and non-normally distributed continuous data will be presented as medians with IQRs (lower quartile to upper quartile). Categorical and ordinal data will be summarised as counts (proportions). The continuous data will be compared using independent Student's t-tests, or Wilcoxon rank-sum test on the basis of distribution of variables; the categorical and ordinal data will be compared by using χ^2, Fisher's exact tests or Kruskal-Wallis test, considering a two-sided significance level of 0.05. The absolute standardised difference (ASD) will be used for the comparison of baseline data between the development and validation cohort, with ASD >0.118 (ie, $1.96 \times \sqrt{(1000+400)/(1000\times 400)}$) considered to be imbalanced.

For the first assessment of unadjusted association between potential predictors and the incidence of PPCs, univariable logistic regression models will be performed. ORs and 95% CIs from these models will also be estimated. Collinearity between categorical variables will be tested with the Cramer *V* test (between nominal variables) and Kendall tau-*b* coefficient (between ordinal variables). Variables with p value less than 0.2 in the unadjusted univariable logistic models and the correlation coefficient between them (collinearity) less than 0.25 will be selected for the inclusion in the multivariable model. Variables with clinical plausibility and extensive reports suggesting a close relationship with PPCs will also be included in the initial multivariable logistic regression, irrespective of their statistical relationship with PPCs. The multilevel multivariable logistic regression model will be constructed using a backward stepwise selection procedure. Potential predictors will be sequentially removed if this exclusion dose not result in a significant change in the log-likelihood ratio test. The cut-off for variable removal will be set at a significance level of 0.05. Adjusted ORs and corresponding 95% CIs will also be calculated. Subsequently, to avoid overfitting and evaluate the stability of development cohort dataset, a bootstrapping method will be deployed for detecting the optimum predictors. A total of 1000 computer-generated samples will be drawn randomly with 1:1 replacement, each including the same number of patients with the development cohort. Within each bootstrap sample, the β coefficient will be calculated using all selected independent variables. The robustness of the model and, thus, the reliability of predictors in the final regression model will be estimated by the 90% CI of the β coefficient derived from

the bootstrap samples. Reliable predictors are anticipated to be retained if the 90% of bootstrap samples indicates statistical significance (p<0.05). The derivative prediction model will be internally validated on the development cohort via bootstrapping (the same as the method mentioned above) to avoid overoptimistic results as with classical internal validation method.

A predictive risk score will be then calculated according to the following formula: $P = e^{a+bX}/1 + e^{a+bX}$, where P is the predictive probability of development of PPCs, e is exponential, a is the intercept of the final model, b is the β coefficient of the logistic regression and X is the value of the variable.

Once derived, predictive performance in both development and validation cohorts will be estimated. Model discrimination (ie, the extent to which patients who develop PPCs will be assigned a higher predicted risk of morbidity than patients who do not develop PPCs) will be estimated using the area under the receiver operating characteristic curve (AUROC), where an AUC of less than 0.5 indicates no discrimination and 1.0 indicates perfect performance. While no irrefutable cut-off value exists, models with an AUC <0.7 may not be suitable for supporting decision making, while values >0.8 provide strong discrimination. Model calibration (ie, the extent that predicted probabilities match observed probabilities) will be evaluated with Hosmer-Lemeshow goodness-of-fit statistic. A calibration plot then will be computed to assess graphically the agreement between the probabilities of developing PPCs as predicted by the internally and externally validated models. Furthermore, the overall accuracy of the model will be assessed with the max-rescaled Brier score, which measures the squared differences between predicted and observed outcomes (for the max-rescaled score, a value approaching 1 denotes a perfect model and a smaller value signifies worse performance).

To increase the readiness of the PATH score, we refer to the ARISCAT score-derived approach.[12] The continuous variables will be categorised according to their tertiles or based on previous cutoffs. Then, a point value will be assigned to each predictor proportional to the estimates from the multivariable logistic regression. For this purpose, we will divide the β estimate of each predictor by the smallest estimate, and the results will be rounded off to define the point values. The simplified scores for development cohort will be added together to produce an overall PPCs risk score for each patient. To evaluate the predictive ability of simplified score model, we will use that score and the minimum description length principle to divide the cohort into three stratums of risk for PPCs: low, intermediate and high, each containing a similar number of patients with a PPC. Finally, to assess the discriminative performance of this risk score in both the development and validation cohorts, we will use the c-statistic, which is also displayed graphically as the AUROC. The Mann–Whitney *U* test will be used to compare postoperative LOS between patients with and without PPCs. The Kruskal-Wallis test will be used to compare postoperative LOS between groups according to the number of PPCs (0, 1, 2–3 or 4 or more). The Kaplan-Meier estimator will be used to analyse trend in mortality rates between patients with and without PPCs, and the differences between groups will be assessed by the log-rank test.

In exploratory analysis, we will evaluate the net benefit of PATH score and ARISCAT score in the complete cohort (1400 patients) via DCA. DCA is an analytic instrument to assess net benefit of a diagnostic tool for which there are competing benefits and harms. The desirable outcome, or 'benefit', is defined as preventive intervention limited to patients with intermediate and high risk for PPCs, while the undesirable outcome, or 'harm', is preventive intervention for low-risk PPCs. In post hoc analysis, we will test the ability of the score in predicting severe PPCs (ie, excluding 'unplanned supplementary oxygen').

The logistic regression analyses, model derivation, accuracy analysis, internal and external validation, exploratory and post hoc analyses will be completed using R statistics V.4.1.2 (R Project for Statistical Computing).

Ethics and confidentiality

Ethical approval has been obtained from the Institutional Review Board of the Affiliated Cancer Hospital and Institute of Guangzhou Medical University, the Second Affiliated Hospital of Guangzhou University of Chinese Medicine and the University of Hongkong—Shenzhen Hospital, respectively. The study has also been registered at Chictr.org.cn with the identifier ChiCTR2100051170. The personal information of the participants will not be disclosed unless authorisation is approved. In addition, each participant will be provided with a unique identity code, the information of which will be properly secured. Anonymised and deidentified data will be shared by request. The CRF and Epidata database will be retained for a minimum of 10 years.

Patient and public involvement

Neither patients nor public representatives were involved in the design, conduct, reporting or dissemination of this study.

Dissemination

The final risk prediction model will be published in an appropriate journal and presented at academic meetings. The investigators who contribute a minimum of 4 months to the trial will be coauthors; otherwise, they will be acknowledged in the publication. Further projects for dissemination and achievements translation include development of an online or app-based calculator or nomogram that will allow direct entry of clinical data to derive personalised predictions for patient care. Future research will be needed to evaluate the effects of preventive strategies centring on risk predictors on the patients' outcome.

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Competing interests None declared.

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