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Association of preoperative spirometry tests with postoperative pulmonary complications after mediastinal masses resection: a protocol for a retrospective cohort study

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2625 words.

ABSTRACT

Introduction Patients with a mediastinal mass are at risk for pulmonary complications in the perioperative period. Preoperative spirometry tests are recommended in patients scheduled for thoracic surgery. Our objective is to investigate the association between preoperative spirometry results and the incidence of postoperative pulmonary complications (PPCs) in patients following mediastinal masses resection, in order to study the usefulness of spirometry tests in the determination of the perioperative respiratory risk.

Methods and analysis The protocol describes a retrospective cohort study of all patients with mediastinal masses in Shanghai pulmonary hospital between 1 September 2021 and 1 September 2022. The primary outcome of this study is the association between preoperative spirometry results and occurrence of postoperative pulmonary complications after mediastinal masses resection. Logistic regression will be used to calculate the adjusted incidence rate difference, incidence rate ratios 95% CI.

Ethics and dissemination The examination and approval documents of the clinical research ethics committee have been received from the ethics committee of our hospital (Shanghai Pulmonary Hospital). The data will be analyzed at ResMan (www.medresman.org.cn/) in linked, anonymized form. On completion, the results of this cohort study will be submitted to a peer--reviewed biomedical journal for publication and presented at several conferences.

Keywords: mediastinal mass, preoperative spirometry tests, postoperative pulmonary complication

Strengths and limitations of this study：

- The study adopts a retrospective cohort study design in a high-volume thoracic center in China.
- The results of the study will inform our understanding about the incidence of PPCs in minimally invasive mediastinal surgery.
- The study will be a single-center study and the generalization of the results may require further validation.

INTRODUCTION

Postoperative pulmonary complications (PPCs) contribute to prolonged length of stay, increased costs of care, and higher operative mortality, which are the leading cause of death after thoracic surgery[1 2]. Pulmonary complications after lung resection have already been established and are well described[3 4]. However, PPCs after mediastinal masses resection in thoracic surgery remain a separate problem, which is rarely concerned by the literature.

Masses of the mediastinum comprise a wide diversity of tumors afflicting patients of all ages[5 6]. Mediastinal masses represent different disease states, from asymptomatic lesions to severe life-threatening presentations[7 8]. For decades, surgical resection has been the preferred therapeutic approach for mediastinal masses[9]. Over the recent years, great advancements in thoracic

surgery, especially the application and popularization of video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), have largely broaden the optional surgical approaches for mediastinal tumor resection. Compared with extensive surgery (thoracotomies and medial sternotomies), these minimally invasive approaches have the superiorities of less trauma, enhanced recovery and fewer perioperative complications[9-12]. However, insufficient studies explore the prevalence of PPCs after mediastinal masses resection and risk factors for its occurrence.

The tumor-caused changes in the mediastinum lead to large variability in the respiratory and hemodynamic responses to anesthesia in patients with mediastinal mass, and even a life-threatening situation may occur due to the deficiency in the preoperative diagnosis, preparation, and anesthetic technique[8 13 14]. Therefore, exploring predictors of general anesthesia risk for patients with a mediastinal tumor is critical and necessary. Accurate assessment of pulmonary function has been claimed to improve risk assessment of pulmonary complications[15 16]. Accordingly, preoperative pulmonary function tests (PFTs) are recommended in patients scheduled for lung resection[17], cardiac[18] or non-thoracic surgery[19], where spirometry, a specialised non-invasive test to measure lung function, may contribute to identifying patients at high risk of postoperative pulmonary complications[20]. Especially, the prognostic value of forced expiratory

volume in 1 s (FEV1) and the ratio of FEV1 to forced vital capacity (FVC) has been rationally well-established in aortocoronary bypass surgery and lung resection, with a reduced FEV1 and FEV1/FVC strongly associated with postoperative mortality and complications[21] [22]. However, the predictive capability of spirometry for mediastinal masses resection surgery is unclear and has never been described in scientific literature.

OBJECTIVES

Primary objective

The primary objective of this study is to investigate the association between preoperative spirometry results and the incidence of PPCs in patients following mediastinal masses resection.

Secondary objective

A secondary objective is to evaluate the prevalence of PPCs after mediastinal masses resection surgery at our center and to determine whether preoperative spirometry is related to 30-day readmission and mortality.

MATERIAL AND METHODS

Study setting

This study will be a retrospective cohort study and will be conducted at Shanghai Pulmonary Hospital, one of the largest thoracic centers in China.

The study was approved by the institutional review board of Shanghai Pulmonary Hospital. The need for obtaining informed patient consent will be waived due to the retrospective nature of this study. We will adhere to the Strengthening the Reporting of Observational Studies in Epidemiology checklist for reporting observational studies. All methods will be performed in accordance to with the ethical principles of the 1964 Declaration of Helsinki and its later amendments. We will use the SPIRIT checklist when writing our report[23].

Patient and eligibility criteria

Patients in receipt of mediastinal masses resection surgery at our center between 1 September 2021 and 1 September 2022 and fulfilling the inclusion criteria will be included in the study (table 1). To be enrolled, only those who underwent preoperative pulmonary function tests will be included in the analysis, and the integrity of the data will be reviewed. A study flow diagram is provided in figure 1.

Table 1 Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
Age≥18 years at time of surgery.	Age≤17 years at time of surgery.
Accept preoperative spirometry test.	Myasthenia gravis (MG).
	Bronchial compression detected by preoperative fiberoptic bronchoscopy.
	Impaired integrity of medical records.
	Metastasectomy cases.
	Surgery using median sternotomy.

Patient and public involvement

Neither patients nor the public was involved in setting the research question or the outcome measures, designing the investigation or interpreting the data. There are no plans to involve patients in the dissemination of the results.

Data collection

Study data will be collected from electronic medical records at our institution from patients who had a mediastinal mass resection under VATS or RATS between 1 September 2021 and 1 September 2022. Metastasectomy cases and those surgery using median sternotomy will be excluded. The following information will be collected from electronic medical records:

Preoperative data

Preoperative data that will be collected are listed in table 2.

Table 2 Preoperative data

Demographic characteristic	Age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, preoperative spirometry results, cardiac function, smoking, cancer cell types, and clinical tumor node metastasis (TNM) stages.
Systematic comorbidities	Hypertension, diabetes mellitus, cardiac disease, cerebrovascular disease, renal dysfunction, and pulmonary disease.
Pre-surgical blood tests	Arterial oxygen partial pressure, peripheral blood hemoglobin content, and inflammatory factor (IL-1β, IL-6 and

	TNF-α) levels.

Intraoperative data

Intraoperative data will include the duration of surgery, blood loss, requirement for transfusion, whether hypoxemia and hypotension occur, new-onset atrial fibrillation, utilization of hydroxyethyl starch, and vasopressors during operation.

Postoperative data

Postoperative data will be collected from the institutional thoracic surgery registry and include PPCs, new-onset arrhythmia, myocardial infarction, renal complication, cerebral infarction, seizure, pulmonary thromboembolism, surgical complications, the length of stay (LOS), 30-day readmission and 30-day mortality. The levels of a myocardial enzyme (cardiac troponin T, creatine kinase MB isoenzyme, myoglobin, and brain natriuretic peptide) and inflammatory factors (IL-1β, IL-6, and TNF-α) in peripheral blood will also be embraced. The renal complication was defined as an Acute Kidney Injury Network classification ≥ 2. Surgical complications will include prolonged air leak (≥ 5 days), prolonged effusion (≥ 5 days), chylothorax, vocal cord palsy, empyema, wound infection, wound dehiscence, and bronchopleural fistula.

Institutional protocol for perioperative care

Patients received standard perioperative care according to our institutional protocol. All patients received general anesthesia, which was performed using standard doses of midazolam, propofol, sufentanil, and rocuronium bromide. Double-lumen tracheal intubation was performed when the patient lost consciousness. The anesthetic, fluid volume, infusion speed, and transfusion were adjusted according to hemodynamic monitoring conditions to maintain the hemodynamic parameters within 20% of the preoperative baseline values. A protective ventilation protocol was implemented for all patients. All patients were routinely extubated at the end of surgery unless the attending anesthesiologists or surgeons decided not to. And for postoperative pain management, we have implemented a protocol specific to each type of patient, mainly relying on patient-controlled intravenous analgesia and giving light intravenous or oral rescue analgesics.

Preoperative spirometry tests

All patients will accept preoperative spirometry tests. Preoperative spirometry results including functional vital capacity (FVC), forced expiratory volume in 1 s (FEV1), %VC (FVC/predicted VC) and FEV1/FVC (FEV1%). FVC is defined as the maximal volume of air exhaled with maximally forced effort from a maximal inspiration, which is the vital capacity performed with a maximally forced expiratory effort.

FEV1 is defined as the volume (L) of air exhaled in the first second of a forced expiration, starting from a position of full inspiration. Both FEV1 and FVC are presented as percentage predicted values based on age, gender, and height reference standards used by our institution, and the ratio of FEV1/FVC is also presented as a percentage. A specialized technician from the Department of Pulmonology will be appointed to perform the spirometry tests for every patient 1 week before surgery.

Main exposures

According to the American Thoracic Society and the European Respiratory Society guidelines[24], the cut-off point for FVC is 80%, and that for FEV1% is 70%. Spirometry assessment is determined by %VC and FEV1%, and subjects are divided into four categories (normal, obstructive, restrictive, and combined), depending on whether %VC and FEV1% are normal or abnormal. Consequently, we will create a normal cohort and a ventilatory dysfunction cohort (including obstructive, restrictive, and combined) (table 3).

Table 3 The cohort of this study

Normal cohort	Ventilatory dysfunction cohort
%VC ≥ 80, FEV1% ≥70 (normal group)	%VC ≥ 80, FEV1% > 70 (obstructive group) %VC < 80, FEV1% ≥ 70 (restrictive group) %VC < 80, FEV1% < 70 (combined group)

%VC: functional vital capacity predicted vital capacity.
FEV1%: forced expiratory volume in 1 s / functional vital capacity.

PPCs

In this study, a PPC will be defined as a circumstance involving newly developed pulmonological symptoms, encompassing asymptomatic atelectasis to respiratory failure according to the definitions of PPCs from European Perioperative Clinical Outcome consensus statement[25] (table 4), which requires medical or interventional treatment.

Table 4 Definitions of postoperative respiratory complications according to European Perioperative Clinical Outcome consensus statement

Postoperative pulmonary complication	Definition
Symptomatic atelectasis	Meet all of the following: (1) a radiological finding of atelectasis in chest X-ray: Lung opacification with shift of hilum, mediastinum, or hemidiaphragm towards affected area and compensatory inflation in adjacent lung. (2) dyspnea. (3) oxyhemoglobin saturation < 90%
Postoperative pneumonia:	Meet all of the following: (1) at least one of the radiological finding of pneumonia on a chest CT or chest X-ray: (i) New or progressive and persistent infiltrates, (ii) consolidation, (iii) cavitation. (2) a fever of ≥38˚C. (3) elevated CRP and WBC levels.
Pleural effusion	at least one of the following finding in chest X-ray: (1) blunting of costophrenic angle. (2) displacement of adjacent anatomical structures. (3) loss of sharp silhouette of ipsilateral hemidiaphragm in upright position. (4) a hazy opacity in one hemithorax with preserved vascular shadows (in supine position).
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura.
Respiratory failure:	Postoperative PaO2 < 8kPa (60mmHg) on room air, a PaO2:FiO2(P/F) ratio <40 kPa (300mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy.

Sample size

To our knowledge, there have been no studies examining rates of PPCs for patients after mediastinal masses resection precisely as we have defined them here. It has been reported that the incidence of PPCs is about 10.5% in adults with mediastinal mass[26]. Based on our pilot study, the incidence of PPCs is about 30% in an abnormal cohort of spirometry tests. Assuming 80% power to detect a proportion of 0.105 in the normal cohort and 0.3 in the abnormal cohort with a one-sided α of 0.05, this would require 300 patients per group, with an overall sample of n=600. We aim to include 660 patients to allow a loss to follow-up rate of 10%. During the 1-year observational windows, there should be approximately 700 patients undergoing mediastinal masses resection surgery in our center, a high-volume thoracic center in China.

Statistical analysis

Descriptive statistics will be mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate for continuous variables and frequency(percentage) for categorical variables. Significant differences between the 2 cohorts were tested by χ^2 or Fischer exact test for categorical variables and Student t-test for continuous variables. Normally distributed data will be compared using nonparametric test. Univariate analysis for odds to any PPCs will be performed by logistic regression for every confounder from our database with a multivariable model built considering

significant ($P < 0.05$) variables from the univariate regression. The results will be shown as odds ratio (OR) [95% confidence interval (95% CI)]. Two-tailed P values of less than 0.05 will be considered statistically significant. All statistical analyses will be performed using Statistical Product and Service Solutions (SPSS) version 26.0 (IBM SPSS Inc., Chicago, IL, USA).

Data Management and Monitoring

All data will be kept through ResMan, an online website for data management. The conduct of the trial conduction will be supervised by the study supervisor (Zongmei Wen), with monthly audits of the trial performed. The datasets will be available from the chief investigator upon reasonable request.

DISCUSSION

Postoperative pulmonary complications (PPCs) encompass a series of respiratory diseases, ranging from asymptomatic atelectasis to respiratory failure[27 28], which are challenging to perioperative management for patients undergoing major surgery, which are relevant to prolonged hospital stays elevated mortality[29]. The incidence of PPCs is multifactorial, varied considerably, and is usually dependent on surgical factors and individual characteristics. Besides, increased age, extensive surgical range, and thoracic surgery are strongly associated with a higher risk of PPCs[29]. The pain disrupting the performance of respiratory muscles and the anaesthesia,

to a lesser extent, adversely affecting lung function are also the causes of PPCs. Advances in perioperative care ensure the diversity of effective interventions covering pre-, intra- and postoperative periods to minimize the adverse effects of surgery and anaesthesia. However, the prediction and treatment of PPCs are multidisciplinary challenges, with infrequent or outdated consensus guidelines aimed to reduce the risk of PPCs compared with those for postoperative cardiovascular complications[30 31].

Accurate assessment of lung function has been regarded as vital for patients presenting for thoracic surgery, which usually have lung or bronchial carcinoma, a mediastinal mass, or esophageal disease. Most of these patients are elderly, with a history of smoking and consequent comorbid conditions. Moreover, unique features of thoracic surgery including the special cardiopulmonary physiology caused by position, ventilation/Perfusion (V/Q) mismatch, one lung ventilation, and hypoxic pulmonary vasoconstriction lead to a large challenge for thoracic anesthesia and perioperative management[32]. All these factors together contribute to the necessity of PFTs. Spirometry is the gold standard method for the detection of airflow limitations and is recommended in patients with chronic obstructive pulmonary disease (COPD) [33]. However, surgery is increasingly being carried out in patients with undiagnosed COPD, which is a major risk factor for PPCs[34]. Anesthesia and surgery may aggravate pre-existing airway obstructions due to the influence on the respiratory

system. FEV1, which predicts the degree of respiratory impairment in patients with COPD, is a critical tool to evaluate a patient for thoracic surgery with preoperative FEV1 less than 60% predicted strongly indicating PPCs and 30-day mortality[35].The value of Spirometry in predicting PPCs after lung resection has been demonstrated by several retrospective studies[19 36-38]. However, the association between spirometry and perioperative respiratory complications in adults with mediastinal mass remains unclear.

One retrospective study evaluated the incidence of life-threatening perioperative respiratory complications in adult patients with mediastinal mass and studied the usefulness of PFTs in the determination of the perioperative risk[39]. A combination of obstructive and restrictive patterns was associated with a high rate of postoperative respiratory complications. However, the patients all had extensive surgery (thoracotomies and medial sternotomies). Currently, minimally invasive surgery has replaced median sternotomy for mediastinal masses and is performed by various approaches. Thus, the primary purpose of this study is to evaluate the association between preoperative spirometry tests and PPCs to provide targets for PPCs prediction in patients scheduled for mediastinal masses resection surgery.

ETHICS AND DISSEMINATION

The examination and approval documents of the clinical research ethics committee have been received from the ethics committee of our hospital (Shanghai Pulmonary Hospital). The data will be analyzed at ResMan (www.medresman.org.cn/) in linked, anonymized form. On completion, the results of this cohort study will be submitted to a peer--reviewed biomedical journal for publication and presented at several conferences.

Contributors Contributors ZZ and FY contributed equally to conceiving this project, facilitating protocol, and drafting this manuscript. Conceptualization: ZZ, FY and ZN; funding acquisition: WZ; investigation and resources: ZZ, FY and YJ; project administration, validation, visualization, writing of the original draft, review and editing: ZZ; supervision: WZ.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Figure 1. Study flow diagram

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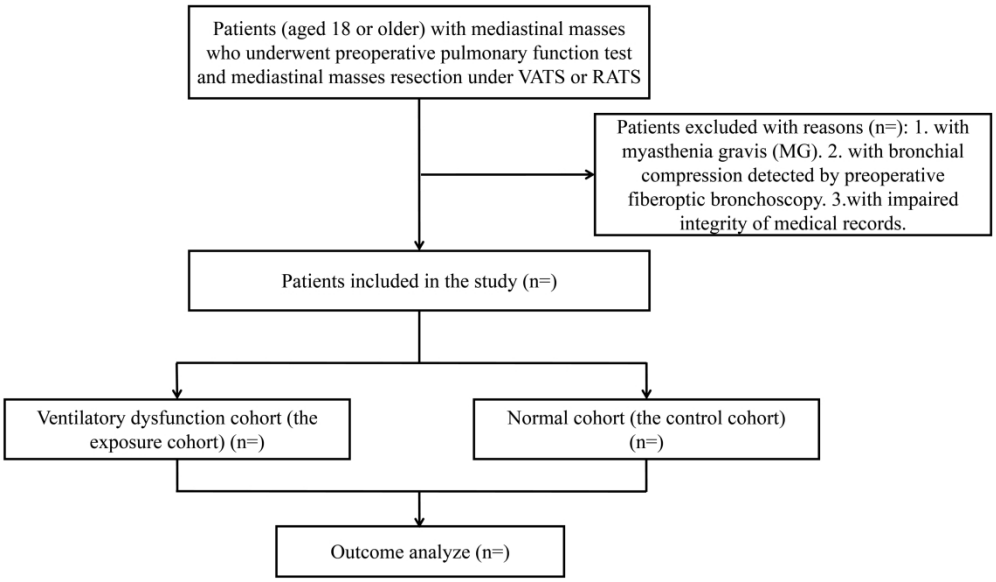

Figure1. Study flow diagram.

316x184mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	15
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5-13

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5-13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5-13
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5-13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5-13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5-13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5-13

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5-13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5-13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	5-13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5-13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	5-13
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5-6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5-13
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	5-13
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	5-13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15-16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	5-13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	5-13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	5-13

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Association of preoperative spirometry tests with postoperative pulmonary complications after mediastinal mass resection: protocol for a retrospective cohort study

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Association of preoperative spirometry tests with postoperative pulmonary complications after mediastinal mass resection: protocol for a retrospective cohort study

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ABSTRACT

Introduction Patients with a mediastinal mass are at risk for pulmonary complications in the perioperative period. Preoperative spirometry tests are recommended in patients scheduled for thoracic surgery. Our objective is to investigate the association between preoperative spirometry results and the incidence of postoperative pulmonary complications (PPCs) in patients following mediastinal mass resection, which may determine the usefulness of spirometry tests in the prediction of the perioperative respiratory risk.

Methods and analysis This protocol describes a retrospective cohort study of patients with mediastinal masses in Shanghai Pulmonary Hospital between 1 September 2021 and 1 September 2022, with a planned sample size of 660 patients. The primary aim of this study is to explore the association between preoperative spirometry results and the occurrence of postoperative pulmonary complications after mediastinal mass resection. Logistic regression analysis will be used to calculate the adjusted incidence rate difference and incidence rate ratios (with 95% CIs).

Ethics and dissemination The study was approved by the ethics committee of Shanghai Pulmonary Hospital (K21-372Y). The results of the study will be submitted to a peer-reviewed biomedical journal for publication and presented at relevant conferences.

Keywords: mediastinal mass, preoperative spirometry tests, postoperative

pulmonary complication

Strengths and limitations of this study

- This is one of the few studies that has evaluated the incidence of postoperative pulmonary complications (PPCs) in patients with mediastinal masses based on preoperative spirometry tests.
- The study adopts a retrospective cohort study design in a high-volume thoracic center in China.
- Multivariate logistic regression following univariate analysis will be used.
- This is a single-center study with unknown generalizability, and validation of the findings will be necessary.
- Residual, unidentified confounding cannot be fully excluded due to the retrospective design of the study.

INTRODUCTION

Postoperative pulmonary complications (PPCs) contribute to prolonged length of stay, increased costs of care, and higher operative mortality, which are the leading cause of death after thoracic surgery[1 2]. Pulmonary complications after lung resection have already been established and are well described[3 4]. However, PPCs after mediastinal mass resection in thoracic surgery remain a separate problem, which is rarely concerned by

the literature.

Masses of the mediastinum comprise a wide diversity of tumors afflicting patients of all ages[5 6]. Mediastinal masses represent different disease states, from asymptomatic lesions to severe life-threatening presentations[7 8]. For decades, surgical resection has been the preferred therapeutic approach for mediastinal masses[9]. Over recent years, great advancements in thoracic surgery, especially the application and popularization of video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), have largely broadened the optional surgical approaches for mediastinal tumor resection. Compared with extensive surgery (thoracotomies and medial sternotomies), these minimally invasive approaches have the superiorities of less trauma, enhanced recovery, and fewer perioperative complications[9-12]. However, insufficient studies explore the prevalence of PPCs after mediastinal mass resection and the risk factors for its occurrence.

The tumor-caused changes in the mediastinum lead to large variability in the respiratory and hemodynamic responses to anaesthesia in patients with mediastinal mass, and even a life-threatening situation may occur due to the deficiency in the preoperative diagnosis, preparation, and anesthetic technique[8 13 14]. Therefore, exploring predictors of general anesthesia risk for patients with a mediastinal tumor is critical and necessary. Accurate assessment of pulmonary function has been claimed to improve risk

assessment of pulmonary complications[15 16]. Accordingly, preoperative pulmonary function tests (PFTs) are recommended in patients scheduled for lung resection[17], cardiac[18], or non-thoracic surgery[19], where spirometry, a specialized non-invasive test to measure lung function, may contribute to identifying patients at high risk of postoperative pulmonary complications[20]. Especially, the prognostic value of forced expiratory volume in 1 s (FEV1) and the ratio of FEV1 to forced vital capacity (FVC) have been rationally well-established in aortocoronary bypass surgery and lung resection, with a reduced FEV1 and FEV1/FVC strongly associated with postoperative mortality and complications[21 22]. However, the predictive capability of spirometry for complications after mediastinal mass resection surgery is unclear and has not been described in scientific literature.

Primary objective

The primary objective of this study is to investigate the association between preoperative spirometry results and the incidence of PPCs in patients following mediastinal mass resection.

Secondary objective

A secondary objective is to evaluate the prevalence of PPCs after mediastinal mass resection surgery at our center and to determine whether preoperative spirometry is related to 30-day readmission and mortality.

METHODS AND ANALYSIS

Study setting

This study will be a retrospective cohort study and will be conducted at Shanghai Pulmonary Hospital, one of the largest thoracic centers in China. The study was approved by the institutional review board of Shanghai Pulmonary Hospital (K21-372Y). The need for obtaining informed patient consent will be waived due to the retrospective nature of this study. We will adhere to the Strengthening the Reporting of Observational Studies in Epidemiology checklist for reporting observational studies. All methods will be performed in accordance with the ethical principles of the 1964 Declaration of Helsinki and its later amendments. We will use the STROBE checklist and guidance when reporting our study findings[23].

Eligibility criteria

Patients in receipt of mediastinal mass resection surgery at our center between 1 September 2021 and 1 September 2022 and fulfilling the inclusion criteria will be included in the study (table 1). To be enrolled, only those who underwent preoperative pulmonary function tests will be included in the analysis, and the integrity of the data will be reviewed. A study flow diagram is provided in figure 1.

Table 1. Inclusion and exclusion criteria	
Inclusion criteria	**Exclusion criteria**
Age≥18 years at the time of surgery.	Age≤17 years at the time of surgery.
Accept preoperative spirometry test.	Myasthenia gravis (MG).
	Bronchial compression was detected by preoperative fiberoptic bronchoscopy.
	Impaired integrity of medical records.
	Metastasectomy cases.
	Surgery using median sternotomy.

Data collection

Study data will be collected from electronic medical records at our institution from patients who had a mediastinal mass resection under VATS or RATS between 1 September 2021 and 1 September 2022. Metastasectomy cases and those surgery using median sternotomy will be excluded. The following information will be collected from electronic medical records:

Preoperative data

Preoperative data that will be collected are listed in table 2.

Table 2. Preoperative data	
Demographic characteristic	Age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, preoperative spirometry results, cardiac function, smoking, cancer cell types, and clinical tumor node metastasis (TNM) stages.
Systemic comorbidities	Hypertension, diabetes mellitus, cardiac disease, cerebrovascular disease, renal dysfunction, and pulmonary disease.

Pre-surgical blood tests	Arterial oxygen partial pressure, peripheral blood hemoglobin content, and inflammatory factor (IL-1β, IL-6, and TNF-α) levels.

Intraoperative data

Intraoperative data will include the duration of surgery, blood loss, requirement for transfusion, whether hypoxemia and hypotension occur, new-onset atrial fibrillation, utilization of hydroxyethyl starch, and vasopressors during operation.

Postoperative data

Postoperative data will be collected from the institutional thoracic surgery registry and include PPCs, new-onset arrhythmia, myocardial infarction, renal complication, cerebral infarction, seizure, pulmonary thromboembolism, surgical complications, the length of stay (LOS), 30- and 90-day readmission, and 30-day mortality. The levels of a myocardial enzyme (cardiac troponin T, creatine kinase MB isoenzyme, myoglobin, and brain natriuretic peptide) and inflammatory factors (IL-1β, IL-6, and TNF-α) in peripheral blood will also be embraced. The renal complication was defined as an Acute Kidney Injury Network classification ≥ 2. Surgical complications will include prolonged air leak (≥ 5 days), prolonged effusion (≥ 5 days), chylothorax, vocal cord palsy, empyema, wound infection, wound dehiscence, and bronchopleural fistula.

Institutional protocol for perioperative care

Patients received standard perioperative care according to our institutional protocol. All patients received general anesthesia, which was performed using standard doses of midazolam, propofol, sufentanil, and rocuronium bromide. Double-lumen tracheal intubation was performed when the patient lost consciousness. The anesthetic, fluid volume, infusion speed, and transfusion were adjusted according to hemodynamic monitoring conditions to maintain the hemodynamic parameters within 20% of the preoperative baseline values. A protective ventilation protocol was implemented for all patients. All patients were routinely extubated at the end of surgery unless the attending anesthesiologists or surgeons decided not to. And for postoperative pain management, we have implemented a protocol specific to each type of patient, mainly relying on patient-controlled intravenous analgesia and giving light intravenous or oral rescue analgesics. All patients underwent routine X-ray examinations on the first day after the operation.

Preoperative spirometry tests

All patients accepted preoperative spirometry tests within 1 week before the operation, which are routine preoperative tests among patients undergoing mediastinal mass resection through VATS or RATS at Shanghai Pulmonary Hospital. Preoperative spirometry results include

functional vital capacity (FVC), forced expiratory volume in 1 s (FEV1), %VC (FVC/predicted VC), and FEV1/FVC (FEV1%). FVC is defined as the maximal volume of air exhaled with a maximally forced effort from a maximal inspiration, which is the vital capacity performed with a maximally forced expiratory effort. FEV1 is defined as the volume (L) of air exhaled in the first second of forced expiration, starting from a position of full inspiration. Both FEV1 and FVC are presented as percentage predicted values based on age, gender, and height reference standards used by our institution, and the ratio of FEV1/FVC is also presented as a percentage. A specialized technician from the Department of Pulmonology in the same centre will be appointed to perform the spirometry tests for every patient 1 week before surgery.

Main exposures

According to the American Thoracic Society and the European Respiratory Society guidelines [24], the cut-off point for FVC is 80% predicted, and that for FEV1% is 70%. Spirometry assessment is determined by %FVC and FEV1%, and subjects are divided into four categories (normal, obstructive, restrictive, and combined), depending on whether %FVC and FEV1% are normal or abnormal. Consequently, we will create a normal cohort and a ventilatory dysfunction cohort (including obstructive, restrictive, and combined) (table 3).

Table 3. Study cohorts	
Normal cohort	**Ventilatory dysfunction cohort**
%FVC ≥ 80, FEV1% ≥70 (normal group)	%FVC ≥ 80, FEV1% < 70 (obstructive group) %FVC < 80, FEV1% ≥ 70 (restrictive group) %FVC < 80, FEV1% < 70 (combined group)
FVC: forced vital capacity. FEV1: forced expiratory volume in 1 s / functional vital capacity.	

PPCs

The PPCs will be assessed via symptoms and the chest X-ray on the first day after surgery. Bedside X-ray examinations are available for every patient to diagnose atelectasis and determine the location of the chest tube, which could assess PPCs. In this study, the PPCs will be defined as the composite of respiratory complications with common pathophysiological mechanisms covering pulmonary collapse and airway contamination[25], which include (i) atelectasis detected on postoperative chest radiograph, (ii) pulmonary aspiration recognized by clear clinical history and radiological evidence, (iii) pneumonia using US Centers for Disease Control criteria[26], and (iv) acute respiratory distress syndrome covering Berlin consensus definition[27] and reinstitution of mechanical or non-invasive ventilation after extubation[28] (table 4). In addition, other complications associated with the physiological changes that follow surgery and anesthesia, including (i) pulmonary embolism, (ii) pleural effusion, (iii) cardiogenic pulmonary oedema, (iv) pneumothorax, and (v) bronchospasm were excluded. Any PPCs defined in table 4 during the

hospital will be recorded. Even if the patient does not complain of symptoms, bedside X-ray examination can help rule out PPCs. The thoracic surgeon decides whether to carry out further CT examination, if necessary, and all the results are available in the electronic medical record.

Table 4. Definitions of postoperative respiratory complications according to the European Perioperative Clinical Outcome consensus statement

Postoperative pulmonary complication	Definition
Atelectasis	a radiological finding of atelectasis in chest X-ray: Lung opacification with shift of hilum, mediastinum, or hemidiaphragm towards affected area and compensatory inflation in adjacent lung.
Pulmonary aspiration	clear clinical history and radiological evidence.
Postoperative pneumonia	**US Centers for Disease Control definition of pneumonia** one chest radiograph with at least one of the following (two or more serial chest X-rays for patients with underlying pulmonary or cardiac disease): (a) New or progressive and persistent infiltrates, (b) consolidation, (c) cavitation; AND at least one of the following: (a) fever (>38°C) with no other recognized cause, (b) leucopaenia (white cell count $<4\times10^9$ litre^{-1}) or leucocytosis (white cell count $>12\times10^9$ litre^{-1}), (c) for adults >70 years old, altered mental status with no other recognized cause; AND at least two of the following: (a) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, (b) new onset or worsening cough, or dyspnoea, or tachypnoea, (c) rales or bronchial breath sounds, (d) worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand).
Postoperative respiratory failure	**Berlin definition of respiratory distress syndrome** Timing: within 1 week of a known clinical insult or new or worsening respiratory symptoms AND…

	Chest imaging: bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules AND… Origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload (requires objective assessment, e.g. echocardiography, to exclude hydrostatic oedema), AND… Oxygenation: mild PaO_2:FiO_2 between 26.7 and 40.0 kPa (200-300 mmHg) with PEEP or CPAP5cmH_2O; moderate PaO_2:FiO_2 between 13.3 and 26.6 kPa (100e200 mmHg) with PEEP 5cm H_2O; severe PaO_2:FiO_2 13.3 kPa (100mmHg) with PEEP 5cmH_2O. **Mechanical ventilation** The need for tracheal reintubation and mechanical ventilation after extubation, and within 30 days after surgery OR mechanical ventilation for more than 24 h after surgery. The inclusion of non-invasive ventilation may be considered on a study by study basis.

Furthermore, the definition of PPCs we used incorporates an assessment of severity[25]:

(i) None: planned use of supplemental oxygen or mechanical respiratory support as part of routine care, but not in response to a complication or deteriorating physiology. Therapies that are purely preventive or prophylactic for example high flow nasal oxygen or continuous positive airways pressure (CPAP) should be recorded as none.

(ii) Mild: therapeutic supplemental oxygen ≤0.6 FiO_2.

(iii) Moderate: therapeutic supplemental oxygen ≥ 0.6 FiO_2, requirement for high-flow nasal oxygen, or both.

(iv) Severe: unplanned non-invasive mechanical ventilation, CPAP, or invasive mechanical ventilation requiring tracheal intubation.

Sample size

To our knowledge, there have been no studies examining rates of PPCs for patients after mediastinal mass resection precisely as we have defined them here. It has been reported that the incidence of PPCs is about 10.5% in adults with mediastinal mass[29]. Based on our pilot study, the incidence of PPCs is about 30% in an abnormal cohort of spirometry tests. Assuming 80% power to detect a proportion of 0.105 in the normal cohort and 0.3 in the abnormal cohort with a one-sided α of 0.05, this would require 300 patients per group, with an overall sample of n=600. We aim to include 660 patients to allow a loss to follow-up rate of 10%. During the 1-year observational window, there should be approximately 700 patients undergoing mediastinal mass resection surgery in our center, a high-volume thoracic center in China.

Statistical analysis

Descriptive statistics were used to characterize the cohort. Categorical variables were described using counts and frequencies, and continuous variables were described using means with standard deviations and medians with interquartile ranges. Significant differences between the 2 cohorts were tested by χ^2 or Fischer exact test for categorical variables and Student t-test for continuous variables. Skewed distributed data will be compared using a non-parametric test.

Logistic regression analysis will be used to calculate the adjusted incidence rate difference and incidence rate ratios (with 95% CIs). Univariate analysis for odds to any PPCs will be performed by logistic regression for every confounder from our database. Furthermore, a multivariable model will be built considering significant ($P < 0.05$) variables from the univariate regression combined with partial pre- and intraoperative variables in the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score[30] (age, preoperative SpO_2, preoperative anaemia, and duration of surgery).

Two-tailed P values of less than 0.05 will be considered statistically significant. All statistical analyses will be performed using Statistical Product and Service Solutions (SPSS) version 26.0 (IBM SPSS Inc., Chicago, IL, USA).

Data management and monitoring

All data will be analyzed through ResMan (www.medresman.org.cn/), an online website for data management, in linked, anonymized form. The conduct of the trial conduction will be supervised by the study supervisor (Zongmei Wen), with monthly audits of the trial performed. The datasets will be available from the chief investigator upon reasonable request.

Study status

Our data collection is ongoing and it is expected to be completed in July 2023. Data analysis is due to begin in August 2023 and we plan to complete

the study by the end of 2023.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

The study was approved by the ethics committee of Shanghai Pulmonary Hospital (K21-372Y). On completion, the results of the study will be submitted to a peer-reviewed biomedical journal for publication and presented at relevant conferences.

DISCUSSION

Postoperative pulmonary complications (PPCs) encompass a series of respiratory diseases, ranging from asymptomatic atelectasis to respiratory failure[31 32], which are challenging to perioperative management for patients undergoing major surgery and relevant to prolonged hospital stays and elevated mortality [33]. The incidence of PPCs is multifactorial, varied considerably, and is usually dependent on surgical factors and individual characteristics. Besides, increased age, extensive surgical range, and thoracic surgery are strongly associated with a higher risk of PPCs[33]. The pain disrupting the performance of respiratory muscles and the anesthesia, to a lesser extent, adversely affecting lung function are also the causes of PPCs. Advances in perioperative care ensure the diversity of effective

interventions covering pre-, intra-, and postoperative periods to minimize the adverse effects of surgery and anaesthesia. However, the prediction and treatment of PPCs are multidisciplinary challenges, with infrequent or outdated consensus guidelines aimed to reduce the risk of PPCs compared with those for postoperative cardiovascular complications[34 35].

Accurate assessment of lung function has been regarded as vital for patients presenting for thoracic surgery, which usually have lung or bronchial carcinoma, a mediastinal mass, or esophageal disease. Most of these patients are elderly, with a history of smoking and consequent comorbid conditions. Moreover, unique features of thoracic surgery including the special cardiopulmonary physiology caused by position, ventilation/Perfusion (V/Q) mismatch, one lung ventilation, and hypoxic pulmonary vasoconstriction lead to a large challenge for thoracic anesthesia and perioperative management[36]. All these factors together contribute to the necessity of PFTs. Spirometry is the gold standard method for the detection of airflow limitations and is recommended in patients with chronic obstructive pulmonary disease (COPD)[37]. However, surgery is increasingly being carried out in patients with undiagnosed COPD, which is a major risk factor for PPCs[38]. Anesthesia and surgery may aggravate pre-existing airway obstructions due to the influence on the respiratory system. FEV1, which predicts the degree of respiratory impairment in patients with COPD, is a critical tool to evaluate a patient for thoracic

surgery with preoperative FEV1 less than 60% predicted strongly indicating PPCs and 30-day mortality[39]. The value of Spirometry in predicting PPCs after lung resection has been demonstrated by several retrospective studies[19 40-42]. However, the association between spirometry and perioperative respiratory complications in adults with mediastinal mass remains unclear.

One retrospective study evaluated the incidence of life-threatening perioperative respiratory complications in adult patients with mediastinal mass and studied the usefulness of PFTs in the determination of the perioperative risk[43]. A combination of obstructive and restrictive patterns was associated with a high rate of postoperative respiratory complications. However, the patients all had extensive surgery (thoracotomies and medial sternotomies). Currently, minimally invasive surgery has replaced median sternotomy for mediastinal masses and is performed by various approaches. Thus, the primary purpose of this study is to evaluate the association between preoperative spirometry tests and PPCs to provide targets for PPCs prediction in patients scheduled for mediastinal mass resection surgery.

This study has several limitations. First, as clinical data were collected from electronic medical records, partially significant data will be lost and some patients will be excluded. However, the high-volume thoracic surgery center ensures sufficient samples and credibility, which covers this

deficiency to some extent. Although the retrospective cohort design will increase case numbers and statistical power, it may lead to selection and information bias. In addition, the study results will have unknown generalizability, in view of the single-center setting, and may not be applicable outside of China. Nevertheless, our results can provide a clinical reference for other centers to predict PPC after mediastinal mass resection.

Contributors ZZ and FY contributed equally to conceiving this project, facilitating protocol, and drafting this manuscript. Conceptualization: ZZ, FY, and ZN; funding acquisition: WZ; investigation and resources: ZZ, FY, and YJ; project administration, validation, visualization, writing of the original draft, review, and editing: ZZ; supervision: WZ.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Figure 1. Study flow diagram

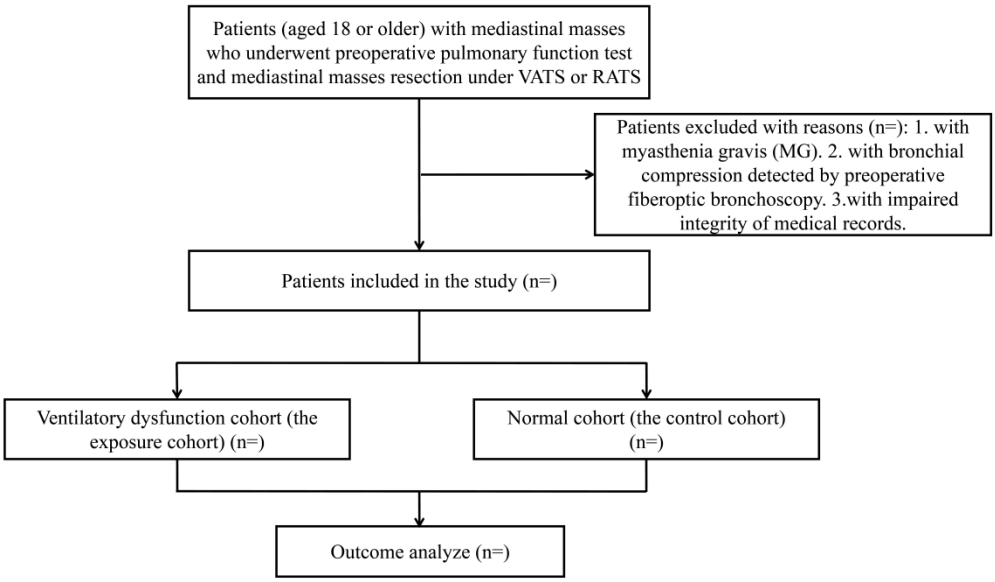

Figure1. Study flow diagram.

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