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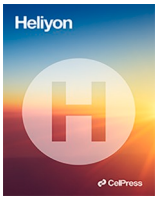

Research article

The efficacy and safety of CT-guided localization of pulmonary nodules by medical adhesives containing methylene blue before surgery

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ABSTRACT

Background: The accurate preoperative localization of pulmonary nodules is essential for a successful video-assisted thoracic surgery (VATS). The aim of this research was to clarify the efficacy and safety of CT-guided localization of pulmonary nodules by mixture of methylene blue and medical adhesive.

Methods: Between January 2020 and January 2021, 103 subjects who have received the CT-guidance pulmonary nodules localization operation were included and retrospectively analyzed. The data on efficiency and complications of preoperative localization using medical adhesives mixed with methylene blue mixture were collected and analyzed.

Results: 103 patients with 111 localized pulmonary nodules were included, 95 of whom had one nodule and 8 of whom had two nodules. The nodule localization success rate reaches as high as 100 %. The mean diameter of pulmonary nodules was 9.50 ± 3.67 mm. The mean distance of pulmonary nodule and pleural surface was 19.95 ± 14.92 mm. The mean depth of localized adhesive in the lung parenchyma was 18.99 ± 11.62 mm, and the mean time required for localization was 16.98 ± 5.72 min. The average time from the nodule localization to VATS surgery was 16.97 ± 7.34 h. The common complications of localization were minor pulmonary hemorrhage (9.74 %) and mild pneumothorax (15.53 %). Besides, pulmonary hemorrhage was related with depths of medical adhesives and nodules in lung parenchyma ($p = 0.018$ and 0.002, respectively).

Conclusion: Medical adhesive mixed with methylene blue is safe and effective in pulmonary nodules localization for VATS, and surgeons have flexibility in scheduling the procedure.

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1. Introduction

Low-dose Computed tomography (CT) is extensively used for screening and follow-up of lung malignant tumors. About 12 % of CT-detected pulmonary nodules of patients at high risk are diagnosed as malignant tumor [1,2]. Thus, the precise and timely diagnosis of

Abbreviations

VATS	Video-assisted thoracoscopic surgery
CT	Computed tomography
ENB	Electromagnetic guided bronchoscopy

pulmonary nodules at high risk is essential. Conventional fine-needle aspiration biopsy is challenging on diagnose due to its insufficient to achieve enough samples or inaccessible to focal tissue sometimes [3]. When those less invasive biopsies fail, VATS can resect pulmonary nodules to obtain more diseased tissue for the accurate pathologic diagnosis [2,3].

Sometimes, the size, location, and density of pulmonary nodule make it's difficult to be located during VATS. Failure to accurately localize pulmonary nodules leads to open chest surgery in up to 54 % of cases [4]. Therefore, how to accurately locate the pulmonary nodule during surgery has become a major problem facing thoracic surgeons. By now, many efforts have been made to localize the pulmonary nodule. Hook wire is a common method for localization, with advantages of 98 % success rate, short localization time, direct intraoperative visibility, and the avoidance of radiation exposure [5]. Nevertheless, the incidence of hook wire dropout is 2.5–13 % [6,7]. Microcoil location is not easily displaced or dislodged, and the incidence of pneumothorax and parenchymal hemorrhage are reduced with microcoil location [8]. The successful rate for the localization by lipiodol is 99 %, but it is associated with a

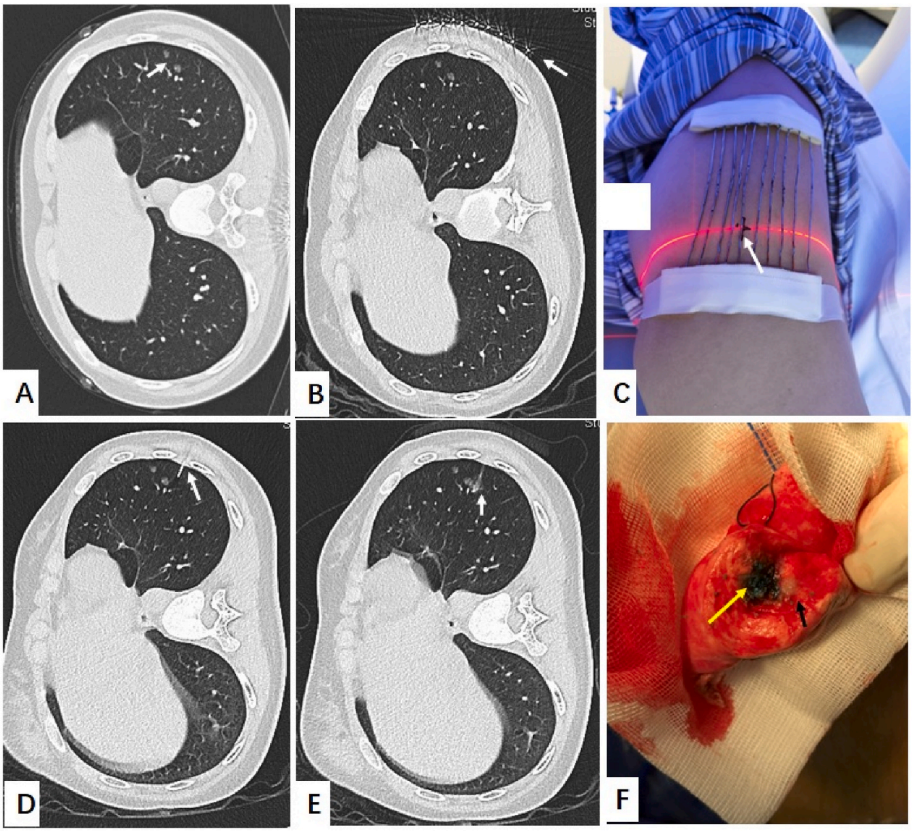

Fig. 1. A 21-year-old female with two pulmonary nodules in the left lower lobe underwent preoperative localization of pulmonary nodules. (A) CT image shows two pulmonary nodules (white arrow) in the left lower lobe. (B) The optimal puncture point was determined under the guidance of CT and with the assistance of the steel needle holder (white arrow). (C) The puncture point is the intersection of the infrared ray at the level of the lung nodule and the steel needle holder (white arrow). (D) The tip of puncture needle (white arrow) was located next to the lesion (white arrow). (E) CT image shows the localization of glue (white arrow) adjacent to the pulmonary nodule. (F) Medical adhesive mixed with methylene blue (yellow arrow) is close to the lung lesion (white arrow) in the resected specimen. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

high pneumothorax rate of 31 % and hemorrhage rate of 12 % [9]. Due to the rapid diffusion on pleural surface, about 13 % of localization by methylene blue is failed, along with the increased pain from pleural irritation by the dye [10,11]. The radioguided localization has high successful rate of pulmonary nodules resection up to 99 % [12], but it requires special equipment, such as CT fluoroscopy, and the operator is faced with potential radiation exposure [13]. Endoscopic ultrasound (EBUS)-guided localization techniques are less complicated than interventional techniques. However, multiple studies have shown a failure rate of 40 %–50 % for localization diagnosis, and its operation requires skilled ultrasound technicians, increasing cost and medical resources [14–16].

Medical adhesives are biologically safe, becoming hard, firm nodules with small spreading area after injection. Therefore, localized adhesive can be accurately palpated during surgery. Methylene blue is an inexpensive and readily available material that diffuses quickly on the lung surface. The mixture of methylene blue and medical adhesive forms a solid blue nodule, which avoids the diffusion of methylene blue and facilitates the identification of pulmonary nodule. Compared with the hook-wire, medical glue combined with methylene blue is founded to be higher success rate, lower complication rate, more safety, and better potential clinical value [17]. In our study, the safety and efficacy of pulmonary nodule localization by the mixture of methylene blue and medical adhesive are evaluated.

2. Patients and methods

2.1. Patient selection and data collection

One hundred and three patients with CT-guided localization for pulmonary nodules between January 2020 and January 2021 were enrolled and retrospective analysis. All patients have performed VATS anatomic segmentectomy, wedge resection or lobectomy after locating the pulmonary nodule with CT-guided medical adhesive mixed with methylene blue. Each localization procedure was discussed with the radiologist prior to preoperative localization. The clinical data of patients were collected and analyzed.

2.2. CT-guided localization method

Preoperative localization: the patient laid on the scanning table and underwent a low-dose CT scan to confirm the accurate localization for pulmonary nodule, after which the thoracic surgeon performed a comprehensive evaluation with a radiologist. The punctured point, needle insertion angle, and length are determined to avoid critical structures (pulmonary vessels, scapula, interlobar fissure and female breast tissue), and the optimal puncture route is confirmed following the shortest puncture route and then the puncture point is marked on skin (Fig. 1A–C). Local anesthesia is then administered, and the puncture is performed using the double-barbed wire system consisting of a 20-gauge needle with a length of 10.7 cm and a BARD DUALOK trocar (Bard Peripheral Vascular) under CT guidance. Once the place of needle tip was confirmed as planned before, the core needle was then taken out (Fig. 1D). A mixture containing 0.2 ml of medical adhesive (Guangzhou Baiyun Medical Adhesive Co. Ltd.) and 0.1 ml of methylene blue (JumpCan Pharmaceutical) is injected into the lung around the nodule through the cannula as quickly as possible (Fig. 1E and F). Since the first injection of medical adhesive quickly seals the cannula, we generally do not carry out a second injection. The distance between the localization adhesive and the pulmonary nodule should be limited to about 1 cm. After successful localization, CT scan was performed again to check for its efficiency and complications, such as hemothorax and pneumothorax (Fig. 2A and B).

2.3. VATS procedure

After successful localization of the pulmonary nodule, a standard two-incision VATS procedure is performed. Generally, the thoracoscopic incision and the surgical incision are placed in seventh and fourth intercostal spaces, respectively. During VATS surgery,

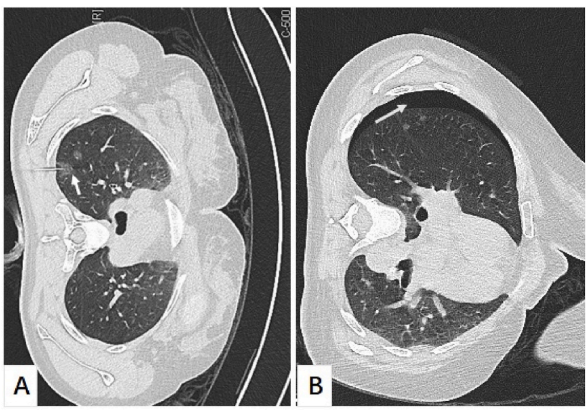

Fig. 2. The complications of preoperative localization of pulmonary nodule. (A) Mild pulmonary hemorrhage was observed in a 41-year female. (B) Moderate pneumothorax was observed in a 26-year female.

the surgeon locates the pulmonary nodule by finger probing the mixed-stained localized adhesive or by methylene blue staining of the pleura (Fig. 3A) and the surgical technique is wedge resection, anatomic segmentectomy or lobectomy. If the pulmonary nodule is next to the lung hilum, lobectomy or segmentectomy is chosen. The surgical specimens were placed and extracted in protective bags, in case of the spread of malignancy. After removal of the lesion, the lung tissue was excised, and a rapid cryosection of excised nodule was performed immediately after silk ligation and marking (Fig. 3B). The incised lung tissue was observed carefully to ensure the complete removal of staining adhesive, avoiding the residual adhesive in the body. The methylene blue staining adhesive allows the surgeon to detect lung lesions easily and quickly.

2.4. Statistical analysis

The data were analyzed by SPSS 26.0 software. The descriptive statistics for continuous variables are presented as mean ± SD. The Pearson correlation analysis was used for the bivariate correlation analysis, and p value less than 0.05 was recognized as significance of difference.

3. Results

3.1. The clinical characteristics of subjects

From January 2020 to January 2021, 103 patients underwent localization of pulmonary nodules with medical adhesive mixed with methylene blue under CT guidance. A total of 111 nodules have been localized, with the average diameter of 9.50 ± 3.67 mm (range: 4–25 mm). Of these, 95 patients had one pulmonary nodule and 8 patients had two nodules. Forty three males and 60 females with average ages of 49.63 ± 13.34 years (range: 21–82 years) were included. The mean length of pulmonary nodule and pleural surface was 19.95 ± 14.92 mm (range: 3–85 mm).

3.2. Perioperative localization of nodules

The mean distance of pleural surface and adhesive was 18.99 ± 11.62 mm (range: 4.9–96.4 mm), the mean preoperative time for the nodule localization was 16.98 ± 5.72 min (range 8–34 min), and the mean time from the end of localization to the beginning of VATS surgery was 16.97 ± 7.34 h (range: 1–48 h). Thirty nine (35.14 %) pulmonary nodules were located in right upper lobes, 5 (4.50 %) in middle lobes, 31 (27.93 %) in right lower lobes, 23 (20.72 %) in left upper lobes and 13 (11.71 %) in left lower lobes.

3.3. Complications after localization

After the pulmonary nodule localization, another CT scan was performed and indicated mild pneumothorax (15.53 %) in 16 patients, without the need for chest tube drainage or obvious symptoms, such as chest pressure or discomfort. Ten patients (9.74 %) had mild parenchymal pulmonary bleeding without clinical significance. No hemothorax, allergies or pulmonary embolism were found. The results showed that minor parenchymal hemorrhage, not the pneumothorax was associated with the depth of local adhesives and pulmonary nodules ($p = 0.018$ and 0.002, respectively, Table 2).

3.4. VATS and postoperative pathology

All pulmonary nodules were distributed locally, and VATS resection was successful in all cases. Among the surgical procedures, wedge resection was performed in 16 cases (15.53 %), anatomic segmental resection in 85 cases (82.53 %), and anatomic lobectomy in

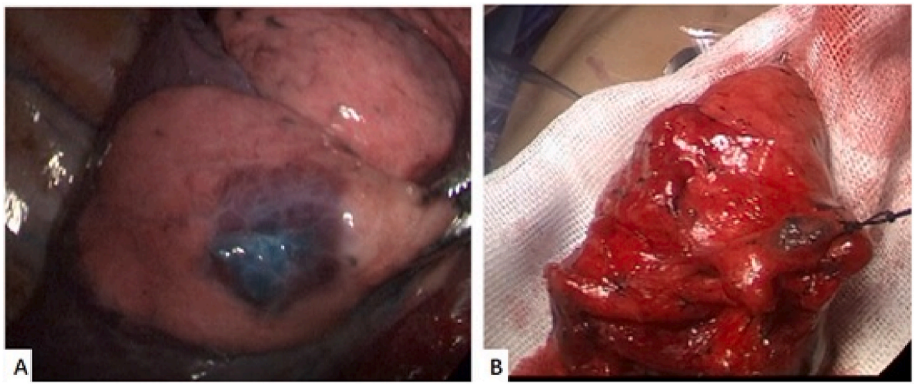

Fig. 3. (A) Pleura was stained with medical adhesive mixed with methylene blue. (B) The lesion was found in excised lung tissue and ligated with silk. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Clinical characteristics of patients with pulmonary nodules.

Characteristics (Mean ± SD)	Medical Adhesive Mixed With Methylene Blue (n = 103)
Gender (n)	
Male/Female	43/60
Age (years)	49.63 ± 13.34
Size of nodules on CT (mm)	9.50 ± 3.67
Nodule Localization (mm)	
Distance to pleural surface	19.95 ± 14.92
Depth within the lung parenchyma	18.99 ± 11.62
Localization duration (min)	16.98 ± 5.72
Localization-to-surgery duration (h)	16.97 ± 7.34
Pulmonary nodule location (n, %)	
RUL	39 (35.14 %)
RML	5 (4.50 %)
RLL	31 (27.93 %)
LUL	23 (20.72 %)
LLL	13 (11.71 %)
Complications of localization procedure	
Minor pneumothorax	16 (15.53 %)
Mild pulmonary hemorrhage	10 (9.71 %)
Histopathologic results	
Chronic inflammation	9 (8.11 %)
Atypical adenomatous hyperplasia	10 (9.01 %)
Adenocarcinoma in situ	11 (9.90 %)
Minimally invasive adenocarcinoma	50 (45.05 %)
Invasive adenocarcinoma	31 (27.93 %)
Surgical type	
Wedge	16 (15.53 %)
Segmentectomy	85 (82.53 %)
lobectomy	2 (1.94 %)

RUL: Right upper lobe; RML: Right middle lobe; RLL: Right lower lobe; LUL: Left upper lobe; LLL: Left lower lobe.

Table 2
The correlation analyses of nodule characteristics and complications.

P value	Nodule distance to pleural surface	Localization adhesive depth within the lung parenchyma
Minor pneumothorax	0.281	0.334
Mild pulmonary hemorrhage	0.002	0.018

2 cases (1.94 %) (Table 1). Postoperative pathology results revealed chronic inflammation in 9 cases (8.11 %), atypical adenomatous hyperplasia in10 cases (9.01 %), adenocarcinoma in situ in 11 cases (9.90 %), minimally invasive adenocarcinoma in 50 cases (45.05 %), invasive adenocarcinoma in 31 cases (27.93 %) and others were identified.

4. Discussion

In this study, the usage of medical adhesives and methylene blue for preoperative localization has the advantage of easily visible and palpable pulmonary nodules during thoracoscopic surgery, with a high success rate of 100 % for localization. As reported, the success rate of micro-coil localization ranged from 93 % to 98.4 % [18], compared with 92 % of methylene blue dye localization [19]. Radio-guided localization techniques displayed consistently high success rates with minimal complications [20]. VATS excision of pulmonary nodules after the radioactive technetium localization achieved nearly 100 % success rates [21,22]. In our study, segmental resection accounted for more than 80 % of VATS surgery, mainly owing to the accurate preoperative localization of the pulmonary nodule. Localization adhesives steadily form firm, rigid nodules within the lung parenchyma, even in case of pneumothorax or excessive body motion after localization.

Common complications of localization procedure are pneumothorax and pulmonary parenchymal hemorrhage. The incidence of pneumothorax for hook wire localization ranged from 7.5 % to 40 %, without serious complications [23]. Methylene blue localization had a higher success rate and fewer complications than hook wire localization. However, VATS needed to be performed quickly, as the dye diffuses rapidly after localization [24]. Micro-coil localization has a 4 %–13 % incidence of asymptomatic pneumothorax [25]. Preoperative localization with lipiodol injection has a 17 % incidence of pneumothorax and drainage is required in 6 % of patients with pneumothorax [26]. Medical adhesives solidify quickly, effectively sealing the puncture point and reducing the complications of pneumatic leakage [27]. In the literature, the incidence of pneumothorax is reported to be 31.9 % when medical adhesive localization is used [28]. The incidence of pneumothorax in our study was11.9 %, slightly lower than that reported in previous literature, and no drainage was required.

Pulmonary hemorrhage is another common complication of localization, with the occurrence rate from 13.9 % to 36 % [28]. The

incidences of parenchymal hemorrhage were 13.9 % and 13.5 % for medical adhesive and hook wire localization procedures, respectively [29]. In previous study, the occurrence rate of pulmonary hemorrhage in localization with hook wire was 22.5 % [30]. In the present study, the incidence of minor pulmonary parenchymal hemorrhage was 13.1 %, which is lower than that of other localization methods. A massive hemothorax or a displaced localization needle can lead to an open chest, lobectomy, or secondary surgery [31]. In our study, there were no serious complications or open thoracotomies.

Previous researches indicate that the depth of the hook wire needle within the lung parenchyma is correlated with the incidence of minor pulmonary hemorrhage [30]. In this study, the pulmonary parenchymal hemorrhage was found to be positively correlated with the depth of localized adhesives and pulmonary nodules, while the pneumothorax was not significantly correlated with depths of localized adhesives and pulmonary nodules. It is understood that the deeper the pulmonary nodule in the lung parenchyma, the higher probability of encountering a pulmonary vessels and thereby high incidence of parenchymal hemorrhage.

Medical adhesive allows for flexibility schedule of preoperative localization of nodules, which facilitates anesthesia preparation and surgical planning. Considering the limitation of respiratory motion and the potential risk of lung laceration and hook wire displacement, the time between hook wire localization and surgery requires to be short, which has been reported to be 1.1 h in general [25]. However, the mean interval was almost extended to one day in our group. Besides, patients experienced little or no pain during the localization procedure, allowing surgeons more time to schedule surgery in this study.

The limitations of our study are nonnegligible. Firstly, this was retrospective study in a single-center, without the randomized controlled design. Secondly, the sample size was small in this study, which may weaken its value on evaluation the effect of localization by mixture of adhesive and dye.

5. Conclusion

The usage of medical adhesives mixed with methylene blue is safe and effective in the preoperative localization of pulmonary nodules for VATS, and facilitates surgeons scheduling the procedure flexibility.

Ethics statement

This study was approved by the Institutional Review Board of Huashan Hospital, affiliated with Fudan University (Permit Number: KY2016-396), and each patient has signed the written informed consent form. The usage of CT images has been approved by the patients.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Informed consent

Project title: Respiratory Disease Biological Sample Library, Huashan Hospital.
Protocol number: KY2016-396.
Version number of protocol: 01, Dec. 16, 2016.
Version number of informed consent form: 01, Dec. 16, 2016.
Study department: Respiratory medicine.
Person in charge: Prof. Shengqing LI.
This notice for subjects will provide you some information about establishment of the Respiratory Disease Biological Sample Library, Huashan Hospital, so as to help you make a decision about whether to agree on its establishment. Your agreement will be completely dependent on your choice. Please read it carefully, and provide any question to the investigators in charge of this study if you have. This protocol has been reviewed and approved by the ethics committee of Huashan Hospital, Fudan University.

Background and objective of establishment of this library

Biological sample library mainly refers to the standardized collection, processing, storage, and application of biological macromolecules, cells, tissues, and organ samples (including human organ tissues, whole blood, plasma, sputum, etc.) of healthy and diseased organisms, as well as clinical, pathological, therapeutic, follow-up, informed consent and other data related to these biological samples, as well as their quality control, information management, and application systems. These biological sample libraries play a very important role in promoting research on diseases.

As important resources for translational medicine research, biological samples have aroused high attention from all the countries increasingly. A feasibility study plan for biological libraries was also launched in Taiwan, China in 2005, in which long-term follow-up was implemented on local common chronic diseases (including common hypertension, diabetes, cancer, etc.), the collected data included participant's health status, history of treatment, lifestyle, living environment, and biological samples, and changes in participant's health were tracked for a long term, so as to carry out research on the genes, environment and their interaction in common chronic diseases. In terms of the research on lung cancer and tuberculosis, multiple biological sample libraries have been currently established at home, e.g., Chinese Cancer Genome, Cancer Resource Bank of Sun Yat-sen University, Beijing Clinical Data and Sample

Resource Library of Major Diseases, Sample Library of Wenzhou Medical College.

The preservation of high-quality biological samples with complete genetic information, combined with the follow-up of clinical data of subjects, and the establishment of an integrated biological sample library, are of great significance for the basic science and clinical translational medicine research on respiratory diseases. The Respiratory Disease Biological Sample Library of Huashan Hospital, Fudan University refers to international standards and utilizes tumor biology, genetics, and medical information resources to conduct a series of basic and clinical studies on the pathogenesis, early diagnosis, treatment of new technologies, and research and development of new drugs for lung cancer, chronic obstructive pulmonary disease, bronchial asthma, pulmonary hypertension, sleep-disordered breathing and pulmonary embolism.

Collection, storage, use and destruction of biological sample: Upon acquisition of informed consent from you, we need to collect your biological samples, the professional staff will draw 8 ml blood from you, and sub-package for cryopreservation after separation of blood components; the collection of lung tissue, bronchoalveolar lavage fluid and sputum is performed on the premise resection and examination are necessary without impact on the diagnosis of disease in medical diagnosis and treatment. After the specimen is isolated, the collected sample will be stored at a low temperature. At the same time, your general data, specimen data and storage location information will be recorded in the cryopreservation management system, the detailed clinical follow-up information will be recorded in the medical record database, and all the acquired radiological data before and after the procedure will be backed up for saving.

The biological sample and clinical and radiological information in the Respiratory Disease Biological Sample Library, Huashan Hospital are valuable resources for conducting scientific research work, the department of respiratory medicine in Huashan Hospital will take charge of proper storage of specimen and data information, and protect your privacy. Your specimen will be used for scientific research only, in accordance with the strict approval procedure, the ethics committee of Huashan Hospital will review the scientific research projects involving biological samples, the sample may be used at home and abroad, and if it is used for an international collaborative research project, the sample may require transfer and export, and may be used for genetic research, we will apply and obtain approval in accordance with the relevant regulations of national human resource management, and make sure that your legitimate rights and interests will not be infringed, including the confidentiality of your personal information, research information you have the right to access and the results with clear clinical application value, the biological sample library management committee will review technical issues related to the use of specimens.

Risks and benefits: ① The biological sample resources and collection of clinical information themselves will not cause harm to human body; ② the collection of blood specimen will be performed strictly in accordance with aseptic requirements, and may have some very small risks, including transient pain and local cyanosis; ③ resection of lung cancer and collection of sputum and bronchoalveolar lavage fluid are normal medical behaviors, it is firstly necessary to make sure that the medical diagnosis and treatment need will not pose additional risks to you; ④ the study will not bring direct benefits to you personally but be beneficial for understanding of the disease, thereby improving clinical diagnosis and treatment technology.

Privacy and confidentiality: The security and confidentiality of personal information will be guaranteed through strict and standardized management of biological sample library. Your specimen will be labeled with the digital study number instead of your name, and the information that can identify you, e.g., name, address and telephone number, and may not be linked to the sample you provide for research. Your personal information will not be revealed to anyone outside the study team, unless your permission is obtained in advance. The investigators may be informed of the genetic information related to the study, demographic information may be provided when the study results are published, however, no any personal information will be disclosed, unless your permission is obtained in advance.

In special circumstances, within the scope specified by laws and regulations, government management departments or members of the ethics committee may access your personal information at the research institution.

Other options and withdrawal from the study: You may choose not to participate in the establishment of the sample library, and your medical treatment, rights and interests will not be affected for that. Even if you agree, you can notify us at any time in the future and request to withdraw. Upon receipt of your written request, we will destroy your specimen in the library and clear your medical record information immediately, however, the study results completed before receipt of your request will be retained.

This study will recruit eligible subjects for long-term enrollment, your biological samples and data will be preserved for a long time, the duration of follow-up will be determined according to the specific research, patients with lung cancer require lifelong follow-up, those with chronic obstructive pulmonary disease and bronchial asthma will be followed up generally for 3–5 years, and the follow-up could be extended based on the specific requirements in the study. This study is very unlikely to be prematurely terminated, and if it is terminated for uncontrollable factors, e.g., natural calamities and political factors, your biological sample and relevant data will be destructed in accordance with the law.

Subject's responsibility Subjects involved in the study are required to fulfill corresponding responsibilities, need to reflect the true data, cooperate with the study content and follow-up as far as possible and report investigators for any discomfort in time and cannot increase or decrease the drugs or treatment methods that affect the study randomly during the study.

For any question about the study, you have the right to ask. If you need to further understand the information about the study, you may contact the Respiratory Disease Biological Sample Library, Huashan Hospital via Xiujuan ZHANG, Telephone: 021–52887072. If there is any question about subject's rights and interests, you may contact the ethics committee of Huashan Hospital, Fudan University via Cuiyun WU, Telephone: 021–52888045.

Expense and compensation : Your participation will not cause any expense beyond your normal medical care. This study adopts the principle of voluntary participation without compensation, i.e., there is no compensation for participation in the Respiratory Disease Biological Sample Library, Huashan Hospital.

Signature of informed consent form

I've read this informed consent form and have the opportunity to ask questions that have been replied.

I understand that participation in the establishment of the Respiratory Disease Biological Sample Library, Huashan Hospital is voluntariness-based. I agree to provide biological samples as stated in this informed consent form.
I agree upon the use of my samples for all the scientific researches, sample transfer, export and use for genetic research.
I understand that I have the right to choose not to participate, or the right to withdraw without discrimination or retaliation upon written notice to investigators in the future, and my medical treatment, rights and interests will not be affected for that.
I will receive a copy of a signed "informed consent form".

CRediT authorship contribution statement

Huijun Zhang: Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Xiujuan Zhang:** Writing – original draft, Project administration, Conceptualization. **Ying Li:** Project administration, Methodology, Formal analysis, Data curation. **Zhifei Huang:** Writing – review & editing, Writing – original draft. **Huahua Liu:** Writing – original draft, Data curation. **Xiaofeng Chen:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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