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ORIGINAL RESEARCH

# Analysis of Fever Following Bronchoscopy and Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Ming Chen, MD; Jinqi Liu, BM; Dongyang Wang, MD; Haipeng Wang, MM; Jinna Liang, BM; Zengjun Li, MM


## ABSTRACT

**Objective** • Bronchoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) are two essential methods for obtaining the pathological diagnosis of central lung masses or hilar and mediastinal lymphadenopathy. We can observe that many patients have a fever after examinations, but the pathogenesis is not yet fully clear. We tried to comprehensively assess the occurrence of postoperative fever and bacterial infections in patients undergoing bronchoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) procedures.

**Methods** • We retrospectively analyzed 512 patients undergoing bronchoscopy or EBUS-TBNA examination. According to examination methods, all patients were classified into three groups: Only perform bronchoscopy examination (BO) group (122 cases), both perform bronchoscopy and biopsy (BB) group (262 cases), and EBUS-TBNA after bronchoscopy (EBUS) group (128 cases). Peripheral blood leucocyte, neutrophil count, and serum IL-6 test results were obtained before and after the examination. A blood culture was performed when the body temperature was higher than 38.5°C.

**Results** • Among the three groups, the onset time (5.5h), average duration (6h), and peak temperature (37.7°C) of fever in the BO group were lower than those in the BB and EBUS groups. Still, there was no significant difference in onset time (11.66h, 11.83h), average duration (12.86h, 13.56h), and peak temperature (39.1°C, 39.1°C) between the BB group and EBUS group. There was no significant difference in the peripheral blood leukocyte count, neutrophil count or IL-6 level before the operation ($P > .05$). Compared with the preoperative, the leukocyte count, neutrophil count and IL-6 level in the three groups were increased after the operation ($P < .05$). Positive blood cultures were diagnosed as normal oropharyngeal flora.

**Conclusions** • Postoperative fever after bronchoscopy is a relatively common complication, most of which do not require special treatment. Individuals with concomitant diseases such as diabetes may have postoperative infections after EBUS-TBNA, and they should be emphatically observed. The findings could potentially extend to similar diagnostic procedures or situations in pulmonary medicine. Understanding the risk factors associated with postoperative fever can help healthcare providers manage patient expectations and monitor certain groups more closely. (*Altern Ther Health Med.* 2024;30(1):254-259).


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## INTRODUCTION

Bronchoscopy is a crucial method to obtain the pathological diagnosis of central lung masses. Bronchoscopy involves the insertion of a slender bronchoscope into the patient's lower respiratory tract via the oral or nasal cavity, enabling direct observation and subsequent treatment of tracheal and bronchial lesions. Bronchoscopy includes rigid bronchoscope and soft bronchoscope, of which soft bronchoscope is also called flexible bronchoscope, and flexible bronchoscope is divided into fiber bronchoscope and electronic bronchoscope.[1,2] Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a valuable modality in the pathological diagnosis of hilar and mediastinal lymphadenopathy caused by cancer,[3] sarcoidosis,[4,5] malignant lymphoma,[6-8] and other diseases. These two examinations are highly accurate, safe, and relatively less invasive. They have been widely used in clinical practice in recent years.[9,10] these procedures are invasive surgeries, and complications have attracted endoscopists' attention.[11-13] If a fever occurs after examination, it is necessary

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to determine the cause of the fever, observe the characteristics of the fever, and determine whether timely intervention is necessary. This can have an impact on the patient's treatment compliance and disease condition judgment. For unknown reasons, previous studies did not separate the patients who underwent bronchoscopy observation alone or combined with biopsy.[14-17] However, in our work, we found that there were differences in fever conditions between patients who underwent bronchoscopy alone and those who received EBUS-TBNA in addition, our analysis also revealed that the two groups' fever rate, peak temperature and duration were different. In addition, when we discuss the incidence of fever or bacteremia, we should consider factors related to routine bronchoscopy examination before EBUS-TBNA, as there is no literature considering the above factors. The purpose of this study was to comprehensively elucidate the fever and bacterial infection rate in bronchoscopy and EBUS-TBNA, understanding the potential impact of postoperative fever and bacterial infections on patient outcomes and the differences between bronchoscopy and EBUS-TBNA. It is important for clinicians to make clinical decision or patient management.

## METHODS

### Patients

A clinical retrospective analysis was conducted for inpatients who underwent bronchoscopy or EBUS-TBNA in the Endoscopy Department of Shandong Cancer Hospital and Institute between May 2018 and May 2020.

### Inclusion and exclusion criteria

Patients were excluded from the analysis if they had at least one of the following conditions: axillary temperature > 38.0°C before the examination; antibiotics, immunosuppressants, or glucocorticoids within 2 weeks; tracheal intubation or mechanical ventilation; other invasive examinations (such as thoracentesis, local lymph node biopsy) or surgery within 48 hours before or after the examination. Fever was defined as an axillary temperature rising above 38.0°C. Finally, 512 patients were included in the analysis.

### Method of bronchoscopy

Patients underwent bronchoscopy according to standard guidelines.[18] Lidocaine (2%) (Shanghai Chaohui Pharmaceutical Co., Ltd, Shanghai, China) was used for nasopharynx, airway anesthesia, and cricothyroid membrane puncture anesthesia. Then, a flexible bronchoscope (BF TYPE1T260, Olympus, Tokyo, Japan) was inserted through the nose. Bronchoscopists decided to perform brushing, biopsy, or other operations based on the clinician's request and bilateral lung condition, or without the above procedures, to only observe the bilateral lungs and then withdraw the bronchoscopes and record the findings. Bronchoscopy alveolar lavage is rarely performed in our department (< 5% per year) and was therefore not included in the analysis.

### Method of EBUS-TBNA

EBUS-TBNA examination is suitable for patients who cannot obtain pathology by bronchoscopy and there is a mass in the hilum or mediastinum. Conventional bronchoscopy was performed before the EBUS-TBNA examination. Operation method: (1) EBUS-TBNA was performed using an ultrasonic bronchoscope (BF-UC260FW; Olympus, Tokyo, Japan) inserted through the nose or mouth. The endoscopic probe was fixed at the predetermined puncture site, and the size and puncture distance of the lesion were measured. (2) The puncture needle (NA-201SX-4021, Olympus, Tokyo, Japan) was abruptly inserted, and an echo was observed in the lesion. (3) The needle core was pulled out, and the negative pressure suction valve was connected and opened while maintaining negative pressure. (4) The puncture needle was moved repeatedly in the lesion, suction was applied approximately 20 times, and the puncture needle was withdrawn.

The puncture was performed with 2 to 7 times according to the specimens obtained.

During the examination, the patient's blood pressure, respiration, heart rate and fingertip percutaneous pulse oxygen saturation ($SpO_2$) were monitored, and oxygen was inhaled to reach $SpO_2 \geq 90\%$.

### Preoperative examinations

These included peripheral blood leucocyte and differential counts, serum IL-6 assays for assessing inflammatory reactions, and chest CT or other imaging examinations.

### Postoperative examination

IL-6 levels were assessed after a 4-hour interval, while the peripheral blood leukocyte count and differential count were examined the next morning. The axillary temperature was monitored at intervals of 6-8 hours over 48 hours, and blood culture was performed when the axillary temperature was higher than 38.5°C. In cases where the patient experienced persistent fever beyond 48 hours or exhibited cough and sputum expectoration symptoms, a chest CT scan was conducted to rule out pneumonia. Additionally, temperature monitoring was continued until it returned to normal.

IL-6 in the serum was measured by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA), which is a quantitative sandwich-type enzyme immunoassay. Peripheral blood was centrifuged at 12 000 r/min for 2 min, the upper clear supernatant was taken, and the expression of IL-6 was detected according to the kit operation procedure. The sensitivity of the IL-6 assay is 0.2–0.4 pg/mL.

### Blood culture

The skin site was initially cleaned with 70% isopropyl alcohol (Nanjing Chemical Reagent Co., Ltd, Nanjing, China), followed by air drying for 30 seconds, and the area was then cleaned with 10% povidone-iodine (Shandong Ruitaiqi Washing and Disinfection Technology Co., Ltd, Dezhou,

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China) for 60 seconds and allowed to air dry for another 60 seconds. Then, an angiocatheter was inserted to collect 20 to 30 mL blood; half of the drawn blood was placed into an aerobic culture bottle, and the remaining half was collected into an anaerobic culture bottle (FX200, BD Company, Franklin Lakes, NJ, USA). Simultaneous acquisition of blood cultures was performed from two distinct anatomical regions. Strain cultivation and identification were subsequently conducted using an automatic blood culture instrument (BACT/ALBRT 3D, BioMerieux company, Lyons, France) and an automatic microbial identification system (VITEK-2, BioMerieux company, Lyons, France). The procedures and results were determined according to the Clinical Laboratory and Standardization Institute (CLSI).

### Definition of bacterial infection

This involved the (1) physician's clinical judgment through a chart review and infection-related disease codes and (2) ED clinical parameters that indicated infection, such as systemic inflammatory response syndrome (SIRS) and the quick sequential organ failure assessment (qSOFA) score. SIRS is defined as a heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute, temperature < 36°C or > 38°C, leukocyte count < 4000 /mm$^3$ or > 12,000 /mm$^3$, and band forms > 10%.[19] The qSOFA score is defined as systolic blood pressure ≤ 100 mmHg, respiratory rate ≥ 22 breaths per minute, and Glasgow Coma Scale <15.[20]

### Definition of positive cultures

Positive culture was defined as at least two bottles of blood culture yielding the same pathogen.[21]

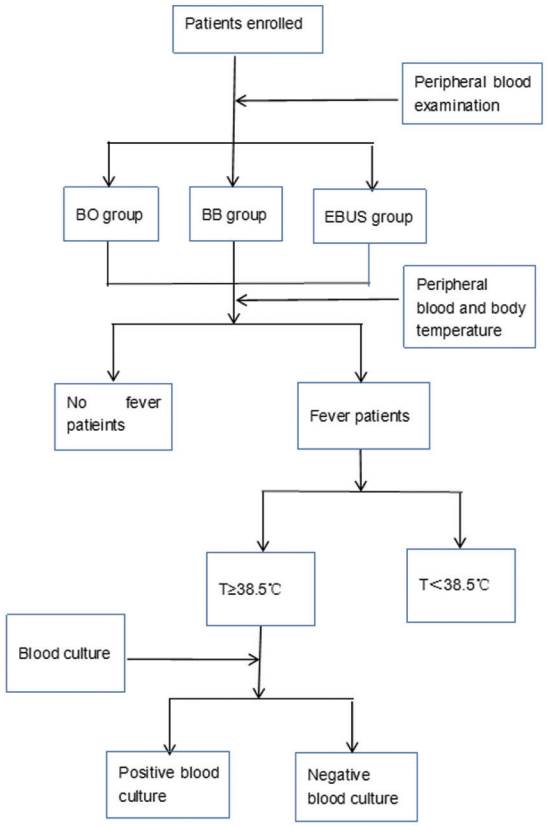
### Definition of contaminants in cultures

(1) There was a single positive blood culture with the growth of pathogens that represent contamination, such as coagulase-negative *staphylococci*, *Corynebacterium* species, *Bacillus* species, *Micrococcus* species, viridans group *streptococci*, and *enterococci*.[21] (2) Microbiological cultures yielded polymicrobial growth without a dominant species. (3) Only one set of organisms frequently found as a contaminant (such as coagulase-negative *staphylococci* or *Bacillus spp*.) was detected. (4) *Bacteremia* was absent, and (5) the patient's clinical course did not correlate with the species identified.

When bacteria were detected in blood cultures, the status of the patient was confirmed by at least 3 physicians in all cases.

All patients were classified into three groups: the bronchoscopy only (BO) group, bronchoscopy and biopsy (BB) group, and EBUS-TBNA after bronchoscopy (EBUS) group. In each group of febrile patients, antibiotics were not given if there was no evidence of infection. Physical cooling or Nonsteroidal Antiinflammatory Drugs (NSAIDs) were administered if the axillary temperature was over 38.5°C. If infection was diagnosed, antibiotics were given according to the result of blood cultures (Figure 1).

**Figure 1.** Study flowchart.




### Statistical analysis

All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) 19.0 (IBM Corp, Armonk, NY, USA). $P < .05$ indicated a significant difference, and $P < .01$ indicated a highly significant difference. The chi-square test was used to compare categorical variables, and the *t* test was used to compare continuous variables. Multiple logistic regression models were used to analyze the odds ratio of fever risk after bronchoscopy and EBUS-TBNA, including age, sex, and prior immunosuppression or antibiotic treatment, which may affect fever after EBUS-TBNA.

## RESULTS

### The baseline clinical characteristics of the patients

A total of 1614 cases were examined, 512 of whom met the study selection criteria. There were 122 cases in the BO group, 262 cases in the BB group, and 128 cases in the EBUS group. Table 1 summarizes the baseline clinical characteristics of the study population. A multivariate model was used to evaluate the risk factors for fever after examination, and no significant differences were found in factors such as age, smoking history, diabetes, previous immunosuppressive therapy, presence or absence of bronchial obstruction or stenosis, or the number of punctured lymph nodes or masses.

### The complication of the three groups

The fever rate, onset time, peak body temperature, fever duration, and peak temperature of the three groups are

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**Table 1.** Risk factors for fever after examination.

| Category | B (95% confidence interval) | *P* value |
|---|---|---|
| Smoking history | 1.082 (0.488-2.403) | .846 |
| Diabetes | 1.823 (0.712-4.663) | .225 |
| Age | 2.043 (0.625-4.861) | .147 |
| Previous immunosuppressants | 1.764 (0.716-4.346) | .232 |
| Bronchial obstruction or stenosis | 2.112 (0.854-5.223) | .118 |
| Number of enlarged lymph nodes or masses | 1.042 (0.369-2.527) | .601 |
| Tuberculosis | 1.904 (0.720-5.036) | .211 |

Note: A multivariate model to evaluate the risk factors for fever after examination and found no significant difference in factors.

**Figure 2.** Fever rate, peak body temperature, onset time, fever duration, and peak temperature of the three groups.

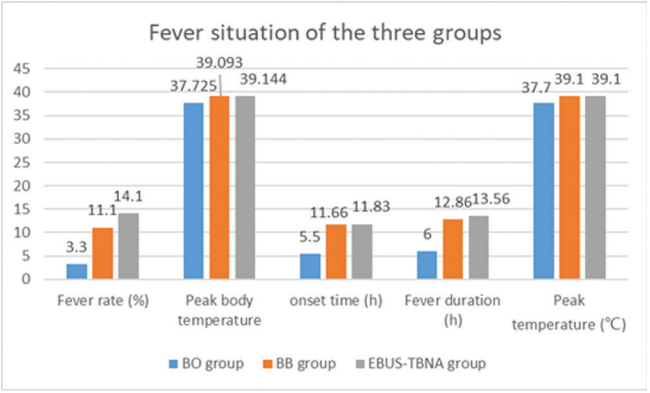



**Table 2.** Peripheral blood leukocytes, neutrophils and serum IL-6 in the three groups

| Groups | Leukocytes (×109/L) | | Neutrophils (×109/L) | | Serum IL-6 (pg/ml) | |
|---|---|---|---|---|---|---|
| | Preoperative | Postoperative | Preoperative | Postoperative | Preoperative | Postoperative |
| BO group | 4.00±0.816 | 8.01±0.816 | 3.25±0.957 | 5.50±0.577 | 4.50±0.577 | 16.25±5.377 |
| BB group | 4.66±0.721 | 18.97±3.896 | 3.66±1.045 | 13.28±2.562 | 4.12±0.942 | 20.52±1.455 |
| EBUS group | 4.78±0.732 | 21.17±3.519 | 3.83±1.098 | 14.94±2.859 | 3.39±1.037 | 22.11±2.220 |

Note: There was no significant difference in the peripheral blood leukocyte count/neutrophil count or IL-6 level before the operation ($P > .05$). Compared with the preoperative leukocyte count/neutrophil count and IL-6 level, the leukocyte count/neutrophil count and IL-6 level in the three groups were increased after the operation ($P < .05$).

**Figure 3.** Changes in IL-6 in the three groups before and after the operation

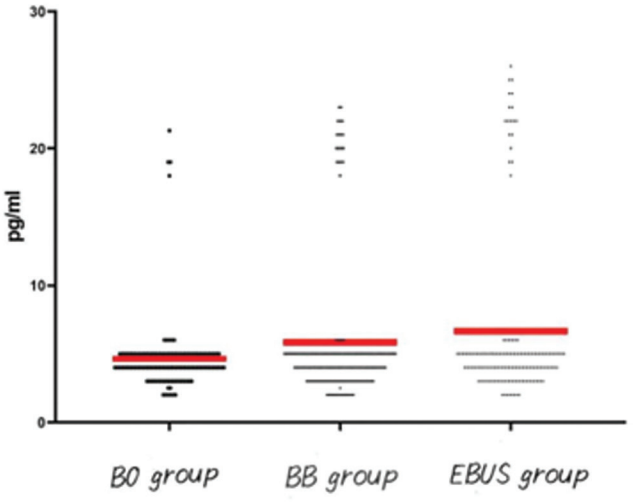
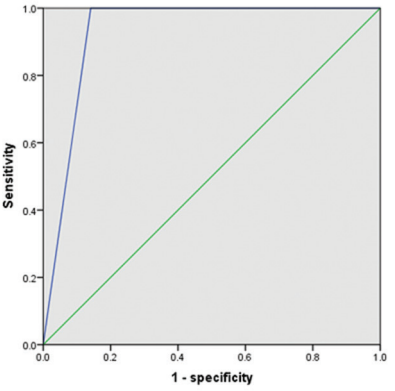



**Figure 4.** ROC curve showing the IL-6 changes for predicting bacterial infection after bronchoscopy.




shown in Figure 2. Among the three groups, the onset time, average duration, and peak temperature of fever in the BO group were different from those in the BB group and EBUS group, but there was no significant difference between the BB group and EBUS group.

### The changes in leukocyte/neutrophil counts and IL-6 levels in the three groups

White blood cells can engulf foreign bodies and produce antibodies, playing an important role in healing body damage and resisting the invasion of pathogens. Detecting serum IL-6 levels can help determine the degree of surgical stress and predict the occurrence of postoperative complications. The changes in leukocyte/neutrophil counts and IL-6 levels in the three groups are shown in Table 2 and Figure 3. There was no significant difference in the peripheral blood leukocyte count/neutrophil count or IL-6 level before the operation ($P > .05$). Compared with the preoperative leukocyte count/neutrophil count and IL-6 level, the leukocyte count/neutrophil count and IL-6 level in the three groups were increased after the operation ($P < .05$). However, the BO group patients had postoperative fever leukocyte/neutrophil counts and IL-6 levels that were all within the normal range. The increases in the leukocyte count/neutrophil count and IL-6 level in patients with postoperative fever in the BB group and EBUS group were beyond the normal range, and this difference was significant ($P < .05$). Although the increases in peripheral blood leukocyte/neutrophil count and IL-6 in the EBUS fever group were higher than those in the BB group, there was no significant difference ($P = .793$ and $P = .671$).

### The diagnostic value of laboratory parameters for predicting bacterial infection after bronchoscopy

To determine the diagnostic value of laboratory parameters for predicting bacterial infection after bronchoscopy, we performed ROC (receiver operating characteristic curve) curve analysis on all patients with fever (n = 51) (Figure 4). The leukocyte level had the highest AUC (Area Under Curve) (0.930; 95% CI (confidence interval), 0.908 to 0.951; $P < .001$).

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**Postoperative infection status of the patients**

A total of 39 sets of blood cultures were collected, 15 of which were positive. The blood culture results of 8 patients in the BB group and 5 patients in the EBUS group were positive for *Actinomyces spp*., *Streptococcus salivarius*, and *Streptococcus mitis*, which were diagnosed as normal oropharyngeal flora. According to clinical observations, none of these 13 persons showed symptoms of infection. One patient in the BB group and one patient in the EBUS group had true positive blood cultures (bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae*) and clinical signs of infection (fever within 9 hours after examination, cough, expectoration). They were diagnosed with bacteremia and received antibiotic treatment, and no further complications were observed. No significant correlation was found between bacteremia and lesion size, number of puncture aspirations performed, or pathology. It is noteworthy that all 2 confirmed bacteremia patients had diabetes.

## DISCUSSION

Many studies have reported that the incidence of fever after bronchoscopy and EBUS-TBNA are approximately 1.2-16% and 10-19.8%, respectively, and our results were 3.3% and 14.1%, respectively. The fever ratio varies greatly among the authors' reports. We believe that this is due to the different selection of cases included, the definition of fever, the method of evaluating fever, and the time interval of measuring body temperature.

Among the three groups, the examination time, lidocaine dosage, and irritation to the tracheal wall were different, Stimulations such as fluid dripping, biopsy, brushing, and piercing can trigger the inflammatory response of the respiratory tract and release inflammatory mediators and endogenous pyrogens such as IL-6. The fever rate, peak temperature and duration exhibited variations across the different groups, which we attribute to the varying doses of cytokines administered. In our study, the BO group necessitated a lesser volume of fluid compared to the BB group, and no external stimuli, such as brushing or biopsy, were applied. Consequently, the release of cytokines was diminished, resulting in a lower proportion of fever and peak temperature. We routinely performed bronchoscopy before EBUS-TBNA. In general, the amount of dripping liquid used by the EBUS group was the same as that of the BB group, and the EBUS group required more time than the BB group. However, the fever incidence and duration in the EBUS and BB groups were not significantly different, indicating that fever was not related to stimulation time but to the amount of stimulation by dripping liquid.

Another explanation for postoperative fever is bacteremia. Bacteremia typically can lead to more severe outcomes or complications. Our study showed that a small number (42/512) of patients' fevers lasted longer than 24 hours, leukocytes and neutrophils increased beyond the normal high limit, antipyretic treatment was ineffective, and the body temperature and leukocyte counts dropped to normal after the addition of antibiotics, suggesting that these fevers were caused by infection. Bronchoscopy may introduce secretions containing pathogenic bacteria from the upper respiratory tract to the lower respiratory tract. Biopsy, brushing or puncture can destroy the tracheobronchial mucosa, and bacteria are more likely to enter the bloodstream through the wound and cause inflammation. Compared with the ordinary bronchoscope, the ultrasound bronchoscope is thicker and more difficult to manipulate, and the front-end video optical system cannot be bent. All these factors increase the chance of contact between the bronchoscope and respiratory mucosa to bring bacteria into the lower airway. In addition, routine bronchoscopy was performed before EBUS-TBNA, and the airway had a double chance of experiencing mucosal damage and exposure to bacteria; consequently, the blood culture had a positive result in the EBUS group. In our study, 2 patients with infection complications had diabetes, and both of them were in the EBUS group, showing that patients with low immunity, such as those with diabetes, were more likely to exhibit secondary infections after bronchoscopy and EBUS-TBNA examination. We observed that the immune status of diabetic patients may have a broader impact on postoperative complications. This discovery guides us to take precautions for diabetic patients who need bronchoscopy and EBUS-TBNA examinations in future work.

All included bronchoscopic, and EBUS-TBNA operations were performed according to standard clinical operating procedures. This study had a single-center design, and the differences in operation experience and operation time between different endoscopists were not considered, they might have influenced the results. Moreover, the sample size of this study was small, in our future research, we will conduct multicenter studies with larger sample sizes to validate the relationship between diabetes and postoperative fever after EBUS-TBNA.

## CONCLUSIONS

The authors believe that postoperative fever after bronchoscopy and EBUS-TBNA is a relatively common complication, and its occurrence may be due to a systemic inflammatory reaction in the body that does not require antibiotic treatment. A small number of cases in patients with concomitant diseases such as diabetes may be complicated by postoperative infections after EBUS-TBNA, so when we assess the risk of postoperative fever and complications, factors such as the type of surgery, patient immunity status cannot be ignored.

### CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

### AUTHOR CONTRIBUTIONS

MC and ZL designed the study and performed the experiments, JLiu and DW collected the data, HW and JLiang analyzed the data, MC and ZL prepared the manuscript. All authors read and approved the final manuscript.

### FUNDING

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## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Committee of Shandong Cancer Hospital and Institute (IRC No. SDTHEC2021012044). All human samples were obtained with informed consent, in accordance with the Declaration of Helsinki.

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