

## Multidisciplinary treatment of thoracic fistulous empyema caused by pulmonary infection: a retrospective study

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### ABSTRACT

**Background:** In cases of thoracic empyema, the presence of a fistula is known to be difficult to treat and associated with a poor prognosis. Few reports have described the management of fistulous empyema caused by lung parenchymal infection. The aim of this study was to describe the outcomes of multidisciplinary management of fistulous empyema caused by pneumonia or lung abscess due to common bacteria and mycobacteria.

**Methods:** Among 108 cases of empyema surgically treated at Kanagawa Hospital over a 10-year period, 14 patients with fistulous empyema due to common bacteria (CBFE) or fistulous empyema due to mycobacteria (MFE) were analyzed. Fistulous empyema due to lung resection was excluded.

**Results:** Eight out of the 9 patients with CBFE and 4 out of the 5 patients with MFE were male. Patients with CBFE were more likely to be >65 years of age ( $p=0.052$ ) and to have a poor performance status ( $p=0.078$ ). The time from onset to first surgical treatment was significantly longer in MFE (median, 5 months;  $p=0.004$ ). Five patients with CBFE and two patients with MFE underwent open window thoracostomy, while three patients with CBFE and four patients with MFE underwent endobronchial occlusion (EBO). Six patients (66%) with CBFE and 3 patients (60%) with MFE achieved fistula closure. Of the patients who underwent EBO, fistula closure was achieved in 3 (100%) of the patients with CBFE and in 2 (50%) of the patients with MFE. Fistula closure was not achieved in any case with non-tuberculous mycobacteria.

**Conclusions:** Fistulous empyema caused by common bacteria or *Mycobacterium tuberculosis* could be cured by surgical treatment and endobronchial intervention with adequate antimicrobial therapy, but fistulous empyema caused by non-tuberculous mycobacteria proved to be intractable. The challenge in the treatment of fistulous empyema due to non-tuberculous mycobacteria is the achievement of bacterial negativity.

**Key words:** fistulous empyema; endobronchial occlusion; common bacteria; non-tuberculosis mycobacteria; tuberculosis.

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**Ethics approval:** This study was approved by the Committee for the Protection of Human Subjects, the Institutional Review Board of the National Hospital Organization, Kanagawa National Hospital (approval no. R3-8; approval date: 11 January 2022). The Institutional Review Board of the National Hospital Organization waived the need to obtain consent for the retrospective compilation, analysis, and publication of the anonymized clinical data.

**Availability of data and material:** The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

**Conflict of interest:** The authors declare that they have no competing interests, and all authors confirm accuracy.

## Introduction

The number of surgeries for empyema has been gradually increasing in Japan, with 2,250 surgeries in 2,012, 2,608 in 2014, and 2,962 in 2017 according to surveys by the Japanese Society of Thoracic Surgeons [1-3]. In patients with empyema, the presence of a fistula represents a factor independently associated with poor prognosis [4]. Guidelines published by the American Association of Thoracic Surgeons and the British Association of Thoracic Surgeons do not provide recommendations for the optimal management of fistulous empyema [5,6].

Fistulous empyema has several causes. They can be broadly divided into those caused by rupture of the pleura due to infection and those that develop after lung resection. Infections can also be divided into those caused by pneumonia or lung abscesses due to common bacteria and those caused by mycobacteria [*Mycobacterium tuberculosis* and non-tuberculous mycobacteria (NTM)]. The optimal treatments of fistulous empyema caused by common bacteria (CBFE) and fistulous empyema caused by mycobacteria (MFE) have not been adequately discussed, although fistulous empyema due to lung resection has been widely reported [7-11]. The aim of this study was to clarify the outcomes of multidisciplinary treatment for CBFE and MFE, excluding fistulous empyema after lung resection.

## Patients and Methods

### Study design and patients

This study was approved by the Committee for the Protection of Human Subjects, the institutional review board of the National Hospital Organization, Kanagawa National Hospital (approval no. R3-8; approval date: 11 January 2022). The need for informed consent was waived due to the retrospective nature of the study and no identifiers of participants present in the manuscript by the Committee for the Protection of Human Subjects, the institutional review board of the National Hospital Organization, Kanagawa National Hospital. All methods were carried out in accordance with relevant guidelines and regulations.

This study investigated 108 patients who underwent surgical treatment under general anesthesia for empyema at our hospital between April 2010 and December 2021. Among these, 8 cases of empyema caused by lung resection and 2 cases of empyema caused by pleurodesis were excluded. Empyema was caused by common bacteria or mycobacteria in 98 cases. Out of these, fistulous empyema was identified in 14 cases, and the clinical presentations, treatment methods, and outcomes were reviewed (Figure 1).

Empyema was defined as septations or loculations identified within the pleural space on computed tomography (CT), the existence of gross pus, or organisms demonstrated on Gram staining or culture, or positive biochemical results. With respect to biochemical methods, if the pH of pleural fluid was less than 7.2, the concentration of glucose in pleural fluid was <40 mg/dL, and the concentration of lactate dehydrogenase in pleural fluid was >1000 IU/dL, empyema was diagnosed biochemically. Class 5 or higher according to the Light classification and the fibrinopurulent stage of the acute pleural empyema classification were included [12]. Surgery was indicated for empyema based on the following: when empyema was diagnosed, antimicrobial agents were administered intravenously, tube thoracostomy drainage was performed and clinical symptoms and images from CT and chest radiography were evaluated within 24 h. If clinical symptoms, fever curves and

white blood cell count in peripheral blood did not improve, surgical treatment was selected. In sputum samples, cases in which tuberculosis, NTM, or fungi were not detected by culture, polymerase chain reaction testing or smear specimens were considered as empyema due to common bacteria. Cases of fistulous empyema after lung resection were excluded because pleural empyema due to lung resection and that due to pneumonia differ substantially in general conditions prior to the onset of empyema.

### Surgical intervention

Surgical treatment was performed according to the following treatment strategy (Figure 2) [4]. If the empyema had no fistula, video-assisted thoracic surgery (VATS) was conducted, with evacuation of the infected fluid, disruption of loculations, and pleural debridement. Intrathoracic lavage through a chest tube was performed for 3-5 days postoperatively with 1000 mL of warm saline solution twice daily for 30 min each time. After two consecutive negative cultures from pleural fluid, the chest tube was clamped and removed if no exacerbation of fever or inflammatory findings was evident for 2 days. If the chest tube was clamped and the patient developed fever or inflammatory findings worsened, the infection was considered uncontrollable. CT was repeated and if the empyema remained, the patient underwent additional VATS. If the pleural fluid culture was not negative and the symptoms of fever and inflammation worsened after the chest tube was clamped, the patient underwent open window thoracostomy (OWT) (Figure 2A). In cases of fistulous empyema, a chest tube was inserted, then VATS was performed and direct closure of the fistula using sutures was attempted. If fistula closure proved unsuccessful, then: i) if the bronchus leading to the fistula was obvious, endobronchial occlusion (EBO) was performed to attempt fistula closure; once the fistula was closed, the patient was treated according to the treatment flow for non-fistulous empyema; and ii) if the bronchus leading to the fistula was unknown or EBO was unsuccessful, OWT was performed. After OWT, EBO or thoracoplasty was considered in each case according to the general condition of the patient (Figure 2B).

Cases of fistulous empyema were categorized as CBFE or MFE. The following factors on admission were compared between groups: age, sex, body mass index (BMI), performance status (PS), hemoglobin A1c, prognostic nutritional index (PNI), neutrophil-to-

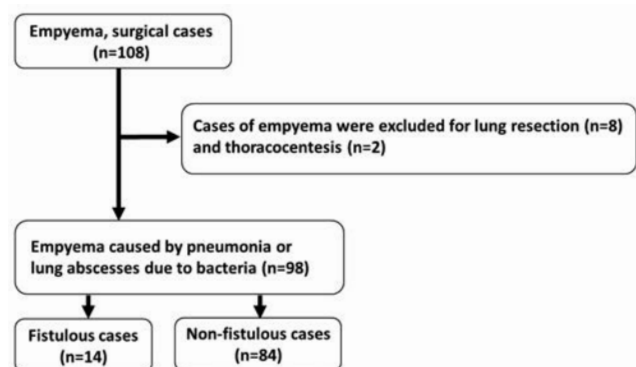


Figure 1. Flow diagram for the present study.

lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and the renal, age, purulence, infection source, and dietary factors (RAPID) score [12-16].

### Definitions of parameters

To assess nutritional status, the BMI and PNI of each patient were evaluated [12,14,15]. BMI was defined as the weight in kilograms divided by the square of the height in meters. Underweight status was defined as BMI <18.5 kg/m<sup>2</sup>. PNI was calculated using the serum albumin concentration and peripheral blood lymphocyte count. PLR and NLR represent indicators of systematic inflammatory response that have been widely investigated as useful predictors of prognosis in patients with infection [12,17]. To describe the level of functioning in terms of the ability of the patient to care for themselves, the Eastern Co-operative Oncology Group definition of performance status was used [13]. To evaluate systemic status, the RAPID score was used [16]. The RAPID score is a clinical score used to identify cases at risk of poor outcomes at presentation among patients with pleural infection. For each patient, renal profile (urea), age, purulence of the pleural fluid, infection source (hospital- vs community-acquired) and dietary factors (albumin) at baseline were used as predictors. Patients were classified into one of three risk groups: i) low risk (RAPID score, 0-2); ii) medium risk (RAPID score, 3-4); or iii) high risk (RAPID score, 5-7) [16].

### Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). All data are expressed as median (interquartile range). Sex was presented as categorical data. Differences between groups were analyzed using the Mann-Whitney U-test for continuous variables and Pearson's  $\chi^2$  test for categorical data. Variables with values of  $p < 0.05$  in univariable analyses were included in the multivariable analysis. Differences with a value of  $p < 0.05$  were considered statistically significant.

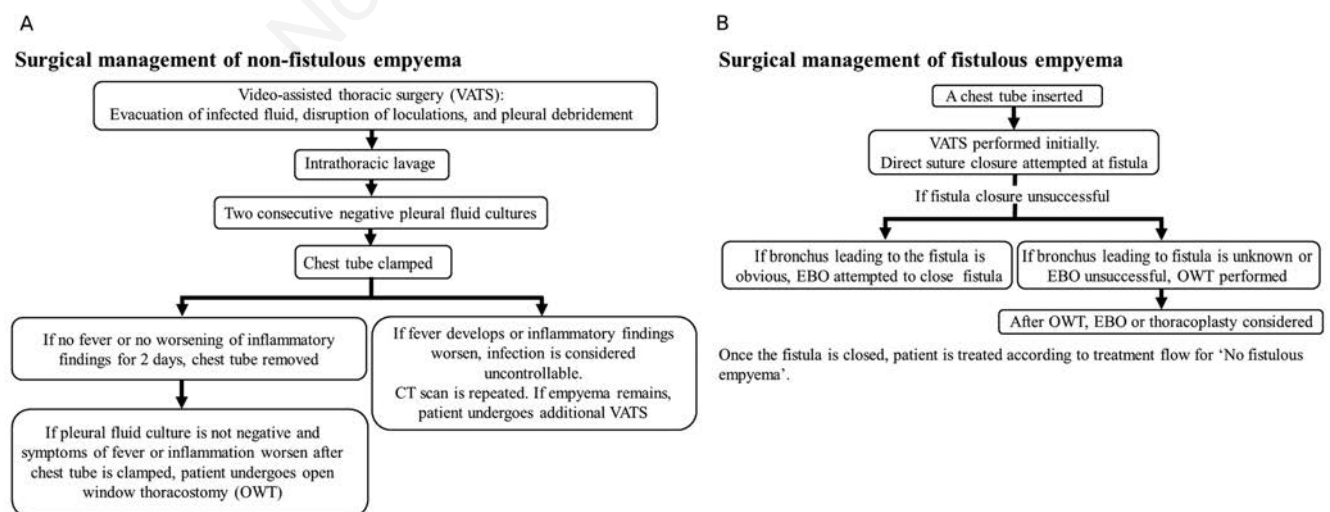
## Results

### Patients

Fourteen patients (12 males) with fistulous empyema (Table 1) were admitted during the study period. Median age was 76 years [interquartile range (IQR), 63-79 years]. Median BMI was 15.6 (IQR, 16.1-19.7). PS was 0-1 in 10 cases and 2-4 in four cases. Median hemoglobin A1c was 6.9% (IQR, 6.3-7.7%), median PNI was 25.7 (IQR, 22.9-31.6) and median PLR was 402 (IQR, 240-392). Median NLR was 7.65 (IQR, 4.66-8.45), and median RAPID score was 3.5 (3-5), comprising scores of 0-2 in 3 cases and 3-7 in 11 cases.

### Treatment of CBFE

Nine cases of CBFE were identified. Details of treatment are summarized in Table 2. The fistula was able to be closed in 6 cases, of whom 5 survived. The remaining patient died of respiratory failure despite fistula closure. In 3 out of the 6 cases with fistula closure, OWT was performed. In two out of the three cases in which OWT was performed, the fistula closed spontaneously after OWT. In 3 cases treated with EBO, the fistula was successfully closed in 2 cases and OWT was avoided. Subsequently, those cases were treated based on the treatment for non-fistulous empyema. The patient who underwent both EBO and OWT showed fistulous empyema due to perforation of a lung abscess in the middle lobe of the right lung. Initially, middle lobectomy and a bronchial stump buttressed with an intercostal muscle flap was performed, but bronchopleural fistula appeared 6 months later. Due to the large size of the fistula, EBO failed to achieve closure. When performing thoracoplasty, rib cartilage was harvested and used for bronchial occlusion to achieve closure of the fistula. In two out of the three cases in which fistula closure was not achieved, OWT was performed. One patient died of respiratory failure, and one died of renal failure. One patient did not consent to OWT and died of respiratory failure. All but one out of the nine patients with CBFE had underlying complications. In 7 out of the 9 cases, surgery was performed promptly in the same month as the onset of fistulous empyema. After surgery, the median time to completion of treatment was 1.25 months.



**Figure 2.** Flow charts for surgical management of non-fistulous empyema (A) and fistulous empyema (B).

## Treatment of MFE

Five cases of fistulous empyema were caused by pulmonary mycobacterial infection. Details of treatment are summarized in Table 3. The organisms responsible were tuberculosis in three cases and NTM in two cases. In the three cases of tuberculosis, the fistulas were successfully closed. Two of these cases involved fistulas in lung tissue destroyed by tuberculosis. Pleuropneumectomy was performed and achieved cure. The times from onset to first surgery were 3 months and 6 months in these cases. The times from initial surgery to end of treatment were 1 month and 4 months. One case involved fistulous empyema caused by perforation of a cavitory lesion due to tuberculosis. OWT, thoracoplasty and plombage with latissimus muscle were performed and the fistula was able to be closed. The time from onset to first surgery was 5 months. The time from initial surgery to the end of treatment was 17 months.

In two cases of pulmonary NTM, the fistula was unable to be closed. One case showed perforation of multiple cavitory lesions just below the pleura, resulting in multiple fistulas. The patient was initially unwilling to undergo OWT and was treated with a chest tube for 22 months. He subsequently underwent OWT, direct suture of the fistula, EBO, thoracoplasty, and muscle flap plombage multiple times. However, closure of the fistula was unsuccessful and he died of respiratory failure 50 months after the initial surgery. One patient did not consent to OWT and strongly requested a single treatment. Segmentectomy (right S2) and bronchial stump buttressing with an intercostal muscle flap were performed, but bronchopleural fistula appeared a month later. The patient did not consent to OWT. Multiple attempts at fistula closure by EBO

proved unsuccessful and she died of respiratory failure 4 months after the first surgery.

## Comparison of CBFE and MFE

A comparison of CBFE and MFE is shown in Table 1. In the 9 cases of CBFE, median age was 77 years (IQR, 76-83 years) and 8 patients were male. In the 5 cases of MFE, median age was 60 years (IQR, 54-74 years) and 4 patients were male. Median BMI was 16.2 kg/m<sup>2</sup> (IQR, 15.7-19.0 kg/m<sup>2</sup>) for CBFE and 19.9 kg/m<sup>2</sup> (IQR, 15.3-20.2 kg/m<sup>2</sup>) for MFE. Three patients with CBFE and 3 patients with MFE were underweight (BMI <18.5 kg/m<sup>2</sup>). Median hemoglobin A1c was 6.9% (IQR, 6.6-7.7 %) with CBFE and 6.8 % (IQR, 6.0-9.0 %) with MFE. RAPID scores were 4 (IQR, 3-5) with CBFE and 3 (IQR, 2-3) with MFE. Successful fistula closure was achieved in 6 patients (66%) with CBFE and 3 (60%) with MFE. OWT was performed in 5 and 2 patients and EBO was performed in 3 and 4 patients with CBFE and MFE, respectively. The interval from onset of fistulous empyema to first surgical treatment was 0 months (IQR, 0-0 months) and 5 months (IQR, 3-6 months) and the interval from initial surgical treatment to end of treatment was 2 months (IQR, 1-2 months) and 4 months (IQR, 4-7 months) with CBFE and MFE, respectively.

## Discussion

Fistulous empyema is reportedly difficult to treat and associated with poor prognosis [4]. The novelty of this study was the focus on the treatment of fistulous empyema caused by pulmonary infec-

**Table 1. Clinical characteristics of patients.**

	Total (n=14)		CBFE (n=9)		MFE (n=5)		p
	Median (IQR) or n (%)	Median (IQR) or n (%)	Median (IQR) or n (%)	Median (IQR) or n (%)			
Sex (male)	12 (86)	8 (89)	4 (80)	0.649			
Age (years)	76 (63-79)	77 (76-83)	60 (54-74)	0.830			
≥65	10 (59)	8 (89)	2 (40)	0.052			
<65	4 (29)	1 (11)	3 (3)				
BMI (kg/m <sup>2</sup> )	15.6 (16.1-19.7)	16.2 (15.7-19.0)	19.9 (15.3-20.2)	0.797			
≤18.5*	8 (57)	6 (67)	2 (40)	0.334			
>18.5 <sup>‡</sup>	6 (43)	3 (33)	3 (60)				
Performance status	0 (0.5-1.75)	1 (0-4)	0 (0-0)	0.112			
0-1	10 (71)	5 (56)	5 (100)	0.078			
2-4	4 (29)	4 (44)	0				
Hemoglobin A1c (%)	6.9 (6.3-7.7)	6.9 (6.6-7.7)	6.8 (6.0-9.0)	0.933			
PNI	25.7 (22.9-31.6)	23.5 (21.1-26.4)	29.4 (26.8-37.4)	0.083			
NLR	7.65 (4.66-8.45)	7.32 (4.99-8.29)	7.98 (2.75-8.50)	0.699			
PLR	402 (240-392)	427 (243-558)	333 (227-385)	0.240			
RAPID score	3.5 (3-5)	4 (3-5)	3 (2-3)	0.147			
0-2	3 (21)	1 (11)	2 (40)	0.207			
3-7	11 (79)	8 (89)	3 (60)				
Open window thoracostomy	7 (50)	5 (56)	2 (40)	0.577			
Endobronchial occlusion	7 (50)	3 (33)	4 (80)	0.803			
Success closing fistula	9 (64)	6 (66)	3 (60)	0.872			
Months from onset to initial surgery	1 (0-2.75)	0 (0-0)	5 (3-6)	0.004			
Months from initial surgery to end of treatment	1 (2-5.5)	2 (1-2)	4 (4-7)	0.240			

\*Underweight; †normal weight and overweight; CBFE, fistulous empyema caused by common bacteria; MFE, fistulous empyema caused by mycobacteria; IQR, interquartile range; BMI, body mass index; PNI, prognostic nutritional index; NLR, neutrocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RAPID, renal, age, purulence, infection source, and dietary factors.

tion. In addition, we divided pulmonary infections into common bacterial infections and mycobacterial infections.

Patients with fistulous empyema were clearly older and with a BMI <18.5 kg/m<sup>2</sup>. However, 71% of cases had a PS of 0-1. This is probably due to the fact that the study was limited to surgical cases. On the other hand, 79% of patients had a RAPID score of 3-7. This suggests that fistulous empyema should be considered one of the most severe pleural infections. Comparisons of patient background between CBFE and MFE showed no significant differences between groups. However, age tended to be younger and PS better with MFE. These findings are consistent with the younger age at which patients are infected with mycobacteria [18]. Diabetes is a known risk factor for the development of empyema and, moreover, has been reported to have an impact on prognosis [19,20]. On the other hand, there are no reports pointing to a clear association between fistulous empyema and diabetes. In the present study, 5 out of 14 cases had a history of diabetes mellitus. The chi-square test showed that the presence or absence of diabetes did not seem to affect the success or failure of treatment or outcome ( $p=0.872$ ) and the success in fistula closure ( $p=0.360$ ). The treatment results

showed no significant difference in the percentage of cases with successful fistula closure between CBFE (66%) and MFE (60%). However, treatments were markedly different. The five CBFE cases in which fistula closure was achieved were all cases with PS 0-1. The cases in which fistula closure proved unsuccessful were limited by poor general condition, including one case with PS 2 and three cases with PS 4. On the other hand, all five MFE cases were PS 0-1. For fistulous empyema due to pulmonary tuberculosis, sufficient antimicrobials (isoniazid, rifampicin, ethambutol and pyrazinamide) were administered to achieve a negative bacterial status. Total pleuropneumectomy was performed in two cases, and OWT, plombage with latissimus muscle and EBO was performed in one case, both resulting in fistula closure. One patient with NTM did not achieve fistula closure despite repeated direct sutures and endobronchial occlusion. In one case, segmentectomy was attempted for a lesion that perforated the cavity, and bronchopleural truncal fistula developed. Because effective antimicrobial agents against NTM remain lacking, the fistula was refractory to closure. In our experience with fistulous empyema caused by NTM, fistula closure has not been achieved. However, reports have

**Table 2. Details of the nine cases of fistulous empyema due to common bacteria.**

Age (years)	Sex	Medical history	PS	Pleural fluid culture	Sputum culture	Outcome	Success in fistula closure	OWT	No. of EBOs	No. of surgeries	Cause of death	Months from onset to first surgery	Months required for treatment
77#1	M	Diabetes mellitus	0	<i>Streptococcus intermedius</i>	<i>Candida albicans</i>	Survival	Success	+	3	9		0	19
76	M	Alcoholic liver disease, cerebral infarction, cataract	1	Negative	<i>Enterobacter cloacae</i>	Survival	Success (spontaneous closure)	+	0	2		0	2
83	M	Diabetes, cerebral infarction, post-operative gastric cancer, post-operative colorectal cancer	0	<i>Klebsiella pneumoniae</i>	<i>Klebsiella pneumoniae</i>	Survival	Success	-	1	2		0	2
54	M	Schizophrenia	0	Negative	Negative	Survival	Success	-	0	1		0	1
87	M	Hearing loss	1	MRSA	MRSA	Survival	Success	-	1	1		0	2
83	M	Diabetes mellitus, hypothyroidism	2	<i>M. avium</i>	$\alpha$ -streptococcus species	Death	Success (spontaneous closure)	+	0	2	Respiratory failure	0	1
79	F	None	4	Negative	<i>Pseudomonas aeruginosa</i>	Death	Failure	+	0	2	Respiratory failure	0	6
76	M	Dementia, post-gastric cancer surgery	4	MRSA	MRSA	Death	Failure	+	0	2	Renal failure	2	2
71	M	Schizophrenia, post-tuberculosis treatment	4	<i>Corynebacterium</i>	<i>Corynebacterium</i>	Death	Failure	-	0	0	Respiratory failure	2	1

CBFE, fistulous empyema caused by common bacteria; PS, performance status; OWT, open window thoracostomy; EBO, endobronchial occlusion; M, male; F, female; MRSA, methicillin-resistant *Staphylococcus aureus*; all cases underwent video-assisted thoracic surgery, with evacuation of the infected fluid, disruption of loculations, and pleural debridement; in patient #1, middle lobectomy and bronchial stump buttressing with intercostal muscle flap was performed initially, but bronchopleural fistula appeared 6 months later; due to the large size of the fistula, EBO failed to achieve closure. When performing thoracoplasty, rib cartilage was harvested and used as a bronchial embolus to achieve closure of the fistula.

**Table 3. Details of the five cases of fistulous empyema due to mycobacteria.**

Age (years)	Sex	Medical history	PS	Pleural fluid culture	Outcome	Success in fistula closure	Surgical procedure	OWT	No. of EBOs	No. of surgeries	Cause of death	Months from onset to first surgery	Months required for treatment
38	M	Miliary tuberculosis	0	<i>M. tuberculosis</i>	Survival	Success	Open window thoracostomy, thoracoplasty and plombage with latissimus muscle	+	1	2		5	17
54	M	Hypertension, diabetes mellitus	0	<i>M. tuberculosis</i>	Survival	Success	Left pleuropneumectomy	-	0	1		6	1
60	M	Duodenal ulcer, Sudden deafness	1	<i>M. tuberculosis</i>	Survival	Success	Left pleuropneumectomy	-	1	3		3	1
74	M	Pulmonary NTM, diabetes mellitus	0	<i>M. avium</i> <i>M. intracellulare</i>	Death	Failure	OWT, EBO, thoracoplasty, and muscle flap plombage	+	2	14	Respiratory failure	22	50
79	F	None	1	<i>M. avium</i>	Death	Failure	A segmentectomy (right S2) and a bronchial stump buttressing with an intercostal muscle flap were performed, but a month later, a bronchopleural fistula appeared.	-	3	3	Respiratory failure	1	4

PS, performance status; OWT, open window thoracostomy; EBO, endobronchial occlusion; M, male; F, female; NTM, non-tuberculosis mycobacterium; S2, Posterior segment; in all cases, sputum and pleural fluid culture results were consistent.

described refractory pneumothorax caused by an NTM in which fistula closure was achieved by performing bronchial occlusion [21,22]. In the case of persistent air leak, fistula closure was successful because no infection had been established in the fistula lesion. The absence of infection is an indication that closure of the fistula is possible. Wound infection represents a well-known obstacle to wound healing in surgical treatment [23,24]. In the treatment of fistulous empyema, fistula closure was difficult to achieve unless the wound infection was controlled first. In our own experience, fistulous empyema caused by common bacteria or tuberculosis could be closed by controlling the fistula infection and combining various treatments, but fistulas caused by NTM, for which effective antimicrobial agents remain lacking, could not be closed due to a lack of infection control. Shiraishi *et al.* reported that lobectomy and total pneumonectomy with NTM were significantly more likely to be followed by bronchopleural fistula than those with multidrug-resistant tuberculosis (MDR-TB) [25]. The definition of MDR-TB is based on resistance to isoniazid and rifampicin [26]. Differences in complications after resection of the lungs for MDR-TB and NTM could be attributed to the fact that other anti-tuberculosis drugs are available besides isoniazid and rifampicin for MDR-TB, whereas effective antimicrobial agents have not been established for NTM. Differences exist in the prevalence of positive sputum culture at the time of surgery between patients with tuberculosis and patients with NTM infections. This is because MDR-TB patients are more likely to respond to antimycobacterial chemotherapy due to individualized multidrug regimens based on drug susceptibility test results. On the other hand, patients with NTM infection tend to undergo pneumonectomy as a last resort due to long-standing disease refractory to medical treat-

ment. In addition, patients with NTM infection have a higher incidence of bronchial stump complications after lung resection [25,27]. The challenge in the treatment of fistulous empyema due to NTM is the achievement of bacterial negativity.

This study has several limitations that need to be kept in mind. First, the number of patients enrolled was small. According to the 2019 annual report by the Japanese Association of Thoracic Surgeons, the prevalence of surgical cases of fistulous empyema was 0.52% (478 cases) out of the total number of surgical cases in general thoracic surgery (91,626 cases). Of all the acute empyema surgery cases (2,597 cases), fistulous empyema accounted for 18.5% of them [28]. In a 13-year period at our institution, 14 out of 1,549 surgical cases had fistulous empyema, resulting in a prevalence rate of 0.90%. Therefore, increasing the number of cases was challenging. Second, because this was a retrospective study, the characteristics of the two groups of patients were not well-matched. Third, the study was conducted in a single institution. The number of cases of fistulous empyema experienced in a single institution is not large, particularly in terms of cases related to NTM. Cases from multiple institutions should be accumulated.

## Conclusions

The present study suggested that poor PS and advanced age may limit the treatment of CBE. When a patient has good PS and is not of advanced age, CBE could be treated using a combination of thoracoplasty, myocutaneous flap plombage, and EBO. Fistulous empyema caused by TB was successfully cured by pleuropneu-

monectomy, thoracoplasty and EBO after adequate antimicrobial treatment. In contrast, cases of NTM could not be converted to a negative infection status by antimicrobial treatment and drainage, and no fistula closure was achieved. Achieving bacterial negativity is the challenge in treating fistulous empyema due to NTM.

## Abbreviations

BMI, body mass index;  
 CT, computed tomography;  
 EBO, endobronchial occlusion;  
 FECB, fistulous empyema caused by common bacteria;  
 FEM, fistulous empyema caused by mycobacteria;  
 IQR, interquartile range;  
 MDR-TB, multidrug-resistant tuberculosis;  
 MRSA, methicillin-resistant *Staphylococcus aureus*;  
 NLR, neutrocyte-to-lymphocyte ratio;  
 NTM, non-tuberculosis mycobacterium.  
 OWT, open window thoracostomy;  
 PLR, platelet-to-lymphocyte ratio;  
 PNI, prognostic nutritional index;  
 PS, performance status;  
 RAPID, renal, age, purulence, infection source, and dietary factors.

## References

- Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery, Masuda M, Kuwano H, Okumura M, Amano J, et al. Thoracic and cardiovascular surgery in Japan during 2012. *Gen Thorac Cardiovasc Surg* 2014;62:734-64.
- Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery, Masuda M, Okumura M, Doki Y, Endo S, et al. Thoracic and cardiovascular surgery in Japan during 2014. *Gen Thorac Cardiovasc Surg* 2016;64:665-97.
- Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery, Shimizu H, Okada M, Tangoku A, Doki Y, et al. Thoracic and cardiovascular surgeries in Japan during 2017. *Gen Thorac Cardiovasc Surg* 2020;68:414-49.
- Sugiura Y, Nakamura M, Fujimoto H, Ochiai H, Ohkubo Y, Fusegawa H, et al. An independent prognostic factor in surgical cases of pleural empyema caused by common bacteria is the presence of a fistula. *Gen Thorac Cardiovasc Surg* 2023. Online ahead of print.
- Shen KR, Bribriesco A, Crabtree T, denlinger C, Eby J, Eiken P, et al. The American Association for Thoracic Surgery consensus guidelines for the management of empyema. *J Thorac Cardiovasc Surg* 2017;153:e129-e146.
- Davies HE, Davies RJO, Davies CWH, BTS Pleural Disease Guideline Group. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. *Thorax* 2010;65:ii41-ii53.
- Massera F, Robustellini M, Pona CD, Rossi G, Rizzi A, Rocco G. Open window thoracostomy for pleural empyema complicating partial lung resection. *Ann Thorac Surg* 2009;87:869-73.
- Wotton R, Garner M, Salem A, Buderer S. Is open window thoracostomy the only method to control infection in patients with an empyema following pulmonary resection for primary lung cancer? *Interact Cardiovasc Thorac Surg* 2021;32:928-32.
- Zanotti G, Mitchell JD. Bronchopleural Fistula and empyema after anatomic lung resection. *Thorac Surg Clin* 2015;25:421-7.
- Asamura H, Naruke T, Tsuchiya R, Goya T, Kondo H, Suemasu K. Bronchopleural fistulas associated with lung cancer operations. Univariate and multivariate analysis of risk factors, management, and outcome. *J Thorac Cardiovasc Surg* 1992;104:1456-64.
- Okuda M, Go T, Yokomise H. Risk factor of bronchopleural fistula after general thoracic surgery: review article. *Gen Thorac Cardiovasc Surg* 2017;65:679-85.
- Tsukioka T, Izumi N, Mizuguchi S, Kyukwang C, Komatsu H, Toda M, et al. Positive correlation between sarcopenia and elevation of neutrophil/lymphocyte ratio in pathological stage IIIA (N2-positive) non-small cell lung cancer patients. *Gen Thorac Cardiovasc Surg* 2018;66:716-22.
- Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.
- Hu Y, Shen J, Liu R, Feng ZM, Zhang CN, Ling L, et al. Prognostic value of pretreatment prognostic nutritional index in non-small cell lung cancer: A systematic review and meta-analysis. *Int J Biol Markers* 2018;33:372-8.
- Lee SI, Ko K-P, Choi CH, Park C-H, Park KY, Son KH. Does the prognostic nutritional index have a predictive role in the outcomes of adult cardiac surgery? *J Thorac Cardiovasc Surg* 2020;160:145-53.e3.
- Rahman NM, Kahan BC, Miller RF, Gleeson FV, Nunn AJ, Maskell NA. A clinical score (RAPID) to identify those at risk for poor outcome at presentation in patients with pleural infection. *Chest* 2014;145:848-55.
- Nakao M, Muramatsu H, Arakawa S, Sakai Y, Suzuki Y, Fujita K, et al. Immunonutritional status and pulmonary cavitation in patients with tuberculosis: A revisit with an assessment of neutrophil/lymphocyte ratio. *Respir Investig* 2019;57:60-6.
- Namkoong H, Kurashima A, Morimoto K, Hoshino Y, Hasegawa N, Ato M, et al. Epidemiology of pulmonary nontuberculous mycobacterial disease, Japan. *Emerg Infect Dis* 2016;22:1116-7.
- Lai SW, Lin CL, Liao KF. Population-based cohort study investigating the correlation of diabetes mellitus with pleural empyema in adults in Taiwan. *Medicine (Baltimore)* 2017;96:e7763.
- Kornum JB, Thomsen RW, Riis A, Lervang H-H, Schönheyder HC, Sørensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. *Diabetes Care* 2007;30:2251-7.
- Okui M, Kohno M, Hasegawa N, Kamiyama I, Ohtsuka T. Intractable pneumothorax treated with endobronchial Watanabe spigots. *J Bronchology Interv Pulmonol* 2016;23:350-3.
- Flora AS, Aragaki-Nakahodo A, Benzaquen S. Endobronchial valve placement for persistent air leaks secondary to pulmonary infections. *J Bronchology Interv Pulmonol* 2021;28:47-52.
- Penhallow K. A review of studies that examine the impact of infection on the normal wound-healing process. *J Wound Care* 2005;14:123-6.
- Robson MC, Stenberg BD, Heggors JP. Wound healing alterations caused by infection. *Clin Plast Surg* 1990;17:485-92.
- Shiraishi Y, Katsuragi N, Kita H, Tominaga Y, Hiramatsu M. Different morbidity after pneumonectomy: multidrug-resistant tuberculosis versus non-tuberculous mycobacterial infection. *Interact Cardiovasc Thorac Surg* 2010;11:429-32.
- World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: Interim policy guidance. 2013. Accessed: cited 2023 Apr 29. Available from: <https://www.who.int/publications/i/item/9789241505482>

27. Shiraishi Y, Nakajima Y, Katsuragi N, Kurai M, Takahashi N. Pneumonectomy for nontuberculous mycobacterial infections. *Ann Thorac Surg* 2004;78:399-403.
28. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery, Minatoya K, Sato Y, Toh Y, Abe T, et al. Thoracic and cardiovascular surgeries in Japan during 2019: Annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg* 2023;71:595-628.

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