

Original Article

Influence of fever on surgical intervention of parapneumonic empyema

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Abstract: Background: Fever is the most common symptom in parapneumonic empyema. However, few studies have investigated the influence of fever on surgical intervention of empyema. This study aimed to evaluate the influence of fever on surgical intervention of empyema. Methods: Patients were divided into two groups according to ear temperature with 38.0°C as a threshold. All patients initially received video-assisted thoracic surgery (VATS), and then open thoracotomy if necessary. Relative variables including between two groups were compared and the predictors of conversion to thoracotomy were analyzed by multivariate analysis. Results: 65.1% of patients presented with fever. Fever was associated with less preoperative chest tube drainage, shorter delay in operation, higher pH and glucose in pleural effusion and earlier stage (all $P < 0.001$). Fever had no influence on the intra-operative and post-operative variables, but patients with fever showed lower rate of conversion ($P < 0.001$). After stratification by conversion, patients with fever could benefit from VATS, particularly in blood loss and operative time. In multivariate analysis, delay in treatment was a predictor of conversion (odds ratio: 1.589, 95% confidence interval: 1.036-2.438, $P = 0.034$); however, fever was a protective factor of conversion (odds ratio: 0.032, 95% confidence interval: 0.001-0.708, $P = 0.029$). Conclusions: Fever is associated with preoperative modality, delay in treatment, pH and glucose in pleural effusion and empyema stage. By contrast, fever is not an inverse predictor of surgery conversion. More fever patients will benefit from minimally invasive surgery.

Keywords: Video-assisted thoracic surgery, parapneumonic empyema, thoracotomy, minimally invasive surgery

Introduction

Parapneumonic empyema (PPE) is defined as the accumulation of pus in the pleural cavity after pneumonia. Currently, the incidence of empyema in the United States is 6 cases per 100,000 persons [1]. Advanced empyema is an indication for surgical intervention according to the Guideline of American College of Chest Physician (ACCP) Parapneumonic Effusion Panel [2]. Traditionally, thoracotomy is performed for the treatment of empyema [3, 4]. Since the introduction of video-assisted thoracic surgery (VATS) in 1990s, VATS has been used to manage empyema achieving comparable efficacy to thoracotomy, even in advanced empyema [5-8].

Conversion to thoracotomy in VATS is an unavoidable topic in the management of empyema. The rate of conversion from VATS to thoracotomy is approximate 0-59% [9-11]. Some cli-

nicians give up the attempt to apply VATS due to the concern on the possible conversion to thoracotomy, and thus many patients will lose the opportunity to be cured by minimally invasive surgery [11]. Thus, the initial attempt of VATS is necessary in the treatment of empyema, if the patients who can benefit from VATS can be predicted. A variety of studies have investigated some factors that can be used to predict the conversion from VATS to thoracotomy in the management of empyema. Delayed referral for surgical intervention is the most common predictor of conversion from VATS to thoracotomy [11-14], and other predictors include location of empyema, pleural thickening and microbiology of pleural effusion [11, 14-16]. PPE is an infectious disease of lower respiratory airway. We hypothesize that, as one of the most common symptoms in PPE patients [11, 16], fever may influence the application of VATS in the treatment of PPE. Some investigators have reported that the rate of conversion from VATS to thora-

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Figure 1. Anterior (A) and lateral (B) view of thermometer. Lateral (C) and anterior (D) view of measurement of ear temperature.



Figure 2. Loculations on CT.

cotomy is higher among fever patients [11]. However, studies involving fever neither delineate the method used to measure the body temperature, nor define the fever according to body temperature. No relative reports can be found regarding the interaction between fever and other characteristics in empyema. This study aimed to evaluate the influence of fever on surgical intervention of empyema.

Patients and methods

Patients and measurement of body temperature

The medical records were retrospectively reviewed in PPE patients who received surgical intervention between January 2008 and January 2015 in our hospital. The inclusion criteria were as follows: empyema was secondary to pneumonia; patients were older than 18 years. Patients with empyema secondary to tuberculosis, trauma, bronchopleural fistulas, postoperative chest injury or malignant lesion were excluded from this study. This study was approved by the Institutional Review Board of Yinzhou People's Hospital.

The right- or left-sided ear temperature was measured as the body temperature with the Braun ThermoScan Type 6021 thermometer (Welch Allyn, Kronberg, Germany) (**Figure 1**). The ear temperature was measured once every 8 h according to the manufacturer's instructions (**Figure 1**). For patients with suspected fever, measurement of body temperature was performed immediately. Once the body temperature was higher than 38.5°C, 0.3 ml of metamizole sodium (Kangqi Pharmaceutical Co., Ltd. Wuhu, China) was administered through the nasal cavity, and the temperature was measured 30 min later and recorded. Once the

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body temperature was lower than 38.5°C, patients were monitored without medicine prescription. According to the body temperature, patients were divided into two groups: fever group (body temperature was higher than 38.0°C at least once daily within two consecutive days prior to operation) and non-fever group. All patients received prophylactic administration of antibiotics and diagnostic thoracentesis or chest tube thoracotomy. The pleural effusion was sampled for biochemical examinations (glucose and PH) and culture of microorganisms. Presence of pus in the pleural cavity and/or positive microbiological culture confirmed the diagnosis of empyema. Additionally, the pH <7.2 or glucose <40 mg/ml in pleural effusion was also helpful for the diagnosis of empyema [2]. Once empyema was diagnosed, VATS was indicated in our clinical practice. Prior to treatment, chest computed tomography (CT) was routinely conducted to assess the severity of intrathoracic disease. The presence of loculation and/or incomplete lung reexpansion (**Figure 2**) detected by CT also served as the indication for surgery. Intrathoracic instillation of fibrinolysis has never been used for the treatment of empyema in our department.

Surgical procedure

VATS as the treatment of empyema in this study was initially attempted in all patients, who underwent double lumen endotracheal intubation on selectively single lung ventilation. Then, the patient was positioned laterally on the operating table with the affected hemithorax upward. The first incision approximate 1.5 cm was made at mid-axillary line 7th or 8th intercostal space, severing as the camera port, through which the surgeon's index finger was introduced to evaluate the intrathoracic adhesion. Once strong adhesion was found, direct conversion to sparing-muscle thoracotomy was conducted; otherwise, the thoracoscope was inserted into the pleural cavity. Further complete exploration of the pleural cavity was needed. The other two incisions were made under the direct VATS visualization: one as working port locating at 4th or 5th anterior axillary line and the other locating at posterior axillary line 7th or 8th intercostal space. The location of incision was determined for the convenience of operation according to CT. The effusion was evacuated, and the thickened parietal

and visceral pleura were removed. If the underlying lung rarely re-expanded well [17], intraoperative conversion to open thoracotomy was employed. The aim of operation, both VATS and open thoracotomy, was to perform satisfactory decortication, which is one of the standards of successful surgery and also the most common cause of conversion to open surgery. At the end of operation, a 32 French chest tube was placed through the camera port and connected to the water-seal system. The patient who was extubated with endotracheal tube in operation room was transferred to ward and receive further treatment; those requiring mechanical ventilation support were admitted to intensive care unit (ICU). Antibiotic therapy continued postoperatively and was adjusted on the basis of microbiological culture of pleural effusion. The chest tube was removed when the fluid volume in daily drainage was less than 150 ml after cessation of air-leakage.

Data collection

The general demographic characteristics were collected. The results of microbiological culture of pleural effusion were recorded in all the patients' Chest CT was routinely performed preoperatively to evaluate the loculations in the pleural cavity and the entrapment of the underlying lung. Perioperative parameters including mortality, morbidity, intra-operative blood loss, operative time (duration between first port incision and completion of wound closure), duration of postoperative drainage, hospital stay, delay in operation (between the onset of symptoms and the referral for surgical intervention), the rate of conversion to open thoracotomy and blood transfusion were recorded or calculated.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation (SD) and categorical variables as frequency (%). The continuous variables were compared using independent-samples student's *t* test, and nonparametric Mann-Whitney U test, or Fisher's exact test if necessary, was used for the comparisons of categorical variables. Univariate and multivariate logistic regression analyses were conducted to evaluate the factors predicting the conversion from VATS to thoracotomy. A value of two-tailed $P < 0.05$ was considered statistically significant.

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Table 1. Characteristics of patients in fever group and non-fever group

Parameters	Fever group	Non-fever group	P
No. (%)	56 (65.1)	30 (34.9)	0.005
Age (yr)	48.5±18.2	47.1±18.3	0.730
Gender (male; %)	42 (75.0)	24 (80.0)	0.603
Loculations (n) ^a			<0.001
Positive	17 (30.4)	23 (76.7)	
Negative	39 (69.6)	7 (23.3)	
Smoking	24 (42.9)	13 (43.3)	0.966
Comorbidity (n) ^b	31 (55.4)	16 (53.3)	0.858
Preoperative intervention			<0.001
Tube thoracotomy	3 (5.4)	11 (36.7)	
Diagnostic thoracentesis	53 (94.6)	19 (63.3)	
Microbiological culture			0.187
Positive	23 (41.1)	8 (26.7)	
Negative	33 (58.9)	22 (73.3)	
Delay in operation, d	8.9±3.8	24.5±10.7	<0.001
pH in effusion	7.26±0.16	7.10±0.23	<0.001
Glucose in effusion	48.27±16.55	34.40±16.52	<0.001

Notes: ^aAssessment by chest CT scan; ^bComorbidities included hypertension, diabetes mellitus, chronic obstructive pulmonary disease and immune compromised disease.

Table 2. Intra-operative parameters in fever group and non-fever group

Parameters	Fever group	Non-fever group	P
Operation time (min)	114.1±22.5	129.8±23.8	0.003
Blood transfusion (n)	0 (0)	1 (3.3)	0.172
Blood loss (ml)	213.0±88.2	325.3±153.3	<0.001
Conversion to open surgery (n)	7 (12.5)	25 (83.3)	<0.001
Stage (n; %)			<0.001
Stage 2	40 (71.4)	7 (23.3)	
Stage 3	16 (28.6)	23 (76.7)	

Statistical analysis was conducted using SPSS version 20.0 (SPSS, Chicago, IL, USA).

Results

A total of 92 patients with PPE received surgical intervention in our department. Six patients were excluded due to poor pulmonary or cardiac reserve, conservative chest tube thoracotomy was performed in 5 patients and repeated thoracentesis in one, but 2 died before discharge and others were discharged with a median hospital stay of 45 days (range: 35-63 days). Ultimately, 86 patients with PPE were

included for final analysis in this study. These patients were successfully treated by either VATS or thoracotomy and received a minimum 6-month follow-up. None died after surgery in the present study. Recurrence of empyema was not observed after surgery. The median age was 48 years (range: 20 to 77 years) and 56 patients were included in fever group. The general characteristics of patients are shown in **Table 1**. The diagnosis of PPE was confirmed by thoracentesis in a majority of patients (83.7%; 72/86).

The patient, who took aspirin orally to prevent thrombosis and was the only one admitted to ICU after surgery, required blood transfusion intraoperatively, suffered from atrial fibrillation and received surgical intervention within 5 days after discontinuation of pharmacotherapy. The blood loss was 1000 ml. Significant differences were observed in most intra-operative parameters between fever group and non-fever group, especially in blood loss, conversion rate and stage ($P < 0.001$; **Table 2**). The reasons for conversion were as follows: inability to insert thoracoscope due to intrathoracic adhesion in 8 (25.0%), failure to fully re-expand the underlying lung in 23 (71.9%) and massive blood loss in 1 (3.1%). After

stratification by conversion, the operative time in patients successfully receiving VATS was 111.8±22.3 min in fever group and 100.2±10.1 min in non-fever group ($P = 0.065$), and the operative time in patients with conversion to thoracotomy was 130.4±17.3 min in fever group and 135.7±21.1 min in non-fever group ($P = 0.549$); however, in both fever group and non-fever group, the operative time in patients receiving thoracotomy was significantly longer than in patients receiving VATS alone (130.43±17.345 min vs 111.8±22.345 min; $P = 0.039$ in fever group and 135.72±21.139 min vs 100.2±10.06 min; $P = 0.001$ in non-

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Table 3. Postoperative parameters in fever group and non-fever group

Parameters	Fever group	Non-fever group	P
Postoperative hospital stay (d)	7.7±3.0	9.1±3.8	0.054
Air leakage (n)	2 (3.6)	5 (16.7)	0.035
Duration of chest tube drainage (d)	4.9±2.5	4.8±3.5	0.664
Postoperative fever days ^a	4.7±2.5	4.5±2.6	0.685

Notes: ^aPostoperative febrile days were defined as days when body temperature was >38 °C at least once daily after surgery.

fever group). Additionally, after stratification by conversion, the intraoperative blood loss showed no significant difference between fever group and non-fever group in patients receiving VATS alone and in those receiving thoracotomy ($P = 0.149$ and $P = 0.057$, respectively). Regarding postoperative variables, air leakage showed significant difference between groups (**Table 3**). After stratification by conversion, air leakage was comparable between fever group and non-fever group in VATS group ($P = 0.885$) and thoracotomy group ($P = 0.447$). No significant differences were observed in the postoperative hospital stay, duration of chest tube drainage and postoperative febrile days between groups after stratification by conversion.

Univariate logistic regression analysis showed the predictive factors for thoracotomy included fever, multiple loculations, delay in operation, glucose of pleural fluid, stage, preoperative intervention and pH of effusion ($P < 0.001$). Only fever and delay in operation were found as independent predictors of thoracotomy in multivariate logistic regression analysis (odds ratio: 0.032; 95% confidence interval: 0.001-0.708; odds ratio: 1.589, 95% confidence interval: 1.036-2.438; $P = 0.034$) (**Table 4**).

Discussion

Fever is the most common symptom in patients with empyema, of whom nearly 71.9-79% have fever [11, 16]. By contrast, few studies have been conducted to investigate the significance of fever in empyema. A recent study showed a higher rate of conversion in the treatment of empyema by VATS in fever patients [11]. However, the method of body temperature measurement was not addressed in this study. The body temperature varies among locations (oral, rectal and ear tempera-

tures). Furthermore, the major aim of this study was not to assess the significance of fever in patients with empyema and thus this issue was not evaluated. We hypothesize that fever as the most common symptom in empyema may influence the therapy of empyema.

In the present study, ear temperature was used as the body temperature. Our results showed

that the rate of conversion from VATS to thoracotomy in fever group decreased when compared with non-fever group ($P \dots$). Interestingly, fever had no influence on the operative time, blood loss and hospital stay. Conversely, fever was association with some pre-operative variables (such as empyema stage, pH and glucose in pleural effusion and loculations on CT).

The body temperature varies between sites at which body temperature was measured even at the same time. Axillary temperature reflects skin temperature, not core temperature and thus is susceptible to the environment temperature [18]. Rectal temperature lags behind the change in core temperature [19]. The ideal site for temperature measurement should reflect both core temperature and immediate change in body temperature. Eardrum meets these criteria and shares the blood supply with the hypothalamus being the temperature control center in the brain [20]. In addition, the measurement of ear temperature is convenient and can be repeatedly performed. Thus, it has been widely used in international airport to detect massive fever [21]. Moreover, patients are more compliant to this measurement [22] and it reflects the actual body temperature. Following the manufacturer's instructions, the body temperature exceeding 38 °C was defined as fever. By this definition, over half of patients (65.1%) in the present study were classified as fever ones (body temperature exceeding 38 °C within two days prior to operation). The proportion of fever patients in the present study was lower than that in previous reports in which only patients with fever were counted before surgery, but the definition and duration of fever were not described [11, 16]. The patients who had fever one day before operation or beyond two days prior to surgery were excluded. It may lead to the decrease in the number of fever

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Table 4. Univariate and multivariate logistic analyses for predictors of conversion to thoracotomy

Parameters ^a	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Fever	0.029 (0.008-0.099)	<0.001	0.032 (0.001-0.708)	0.029
Multiloculations	37.788 (9.692-147.332)	<0.001	12.408 (0.669-230.151)	0.091
Delay in operation	1.565 (1.251-1.956)	<0.001	1.589 (1.036-2.438)	0.034
Glucose in effusion	0.313 (0.176-0.555)	<0.001	0.459 (0.052-4.048)	0.484
Stage	13.667 (4.618-40.445)	<0.001	0.034 (0-7.399)	0.218
Preoperative intervention	15.6 (3.203-75.987)	<0.001	1.094 (0.078-15.362)	0.947
pH in effusion	0.006 (0-0.103)	<0.001	0.054 (0-160.86)	0.474

Notes: ^aOnly parameters showing significant difference in univariate analysis were presented. OR = odds ratio; CI = confidence interval.

patients which also explains the lower proportion of fever patients in the present study.

Of interest, our results showed fever was a predictor of conversion from VATS to thoracotomy in the management of empyema, which has never been reported. Some investigators report a higher rate of conversion in fever phase with a maximal rate of 59% [11]. There is still controversy on the surgical intervention of empyema. Even in ACCP guideline, no ideal technique has been recommended [2]. However, since last 1990s, increasing thoracic surgeries have been completed by VATS for lung diseases, including empyema. Direct thoracotomy may result in the loss of opportunity of minimally invasive therapy in empyema patients, because the success rate of minimally invasive therapy can reach 41%, even 100% in previous studies [9-11]. Thus, all patients initially underwent VATS, as reported in earlier studies [8, 11]. Nevertheless, conversion is an unavoidable issue in VATS of empyema. Previous studies have investigated the predictor of conversion, including the delay in operation, results of bacterial culture, thickening of pleura and loculations [11-16]. Another factor assessed is fever [11], which was further investigated in our study. Our results showed that the rate of conversion decreased in fever patients when compared with non-fever group, which might be related to the definition of fever in our study. In addition, in fever patients, delay in operation was shorter and earlier stage was found, which may increase the success rate of VATS.

The examination of pleural effusion is of importance in the pre-operative diagnosis of empyema, particularly the glucose and pH in the pleural fluid. The glucose and pH in the pleural

effusion were measured in all the patients. We speculated that glucose and pH were sufficient to confirm the diagnosis of empyema, as reported in recent studies that either lower glucose or lower pH in pleural effusion may confirm the diagnosis of empyema [2, 16, 17]. Furthermore, an association of higher glucose and pH in effusion with fever was established in our study. However, the reason for this relationship is still unclear and further study is warranted. In addition, ultrasound examination has also plays an important role in the diagnosis of empyema and can determine the septae [16, 23]. However, ultrasound examination cannot determine the lesion of pulmonary parachyma and thus not applicable as a routine technique in clinical practice. CT can also be used for pre-operative assessment of empyema. The pleural thickening on CT is an indicator of conversion [11], but the measurement of pleural thickening is complex [11, 24, 25]. In contrast, the evaluation of pleural loculations on CT is simple and direct [11, 16] and thus is the most important radiological assessment which was used in the present study. On the basis of our findings, lower incidence of pleural loculations was found in patients with fever, which might be ascribed to the earlier stage and shorter delay in operation in fever group.

Although the association between fever and some pre-operative parameters was demonstrated in our study, no significant difference was found between fever and non-fever group regarding the perioperative parameters, including the hospital stay, blood loss and postoperative febrile duration. Particularly, the outcome after surgery was significantly different between fever group and non-fever group, which was not observed after stratification by conversion

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(VATS vs thoracotomy). In previous studies, VATS has the advantage of less blood loss and shorter hospital stay [6, 8, 11, 15]. Thus, we speculate that surgical approach may be a confounding factor in our study, which was confirmed after the stratification by surgical approach. Thus, fever has no influence on the outcome of surgical therapy in empyema.

There are some limitations in our study. First, this was a retrospective study, and the selection bias could not be fully eliminated. In addition, there was a small sample size in this study. Finally, ear temperature of 38°C as the criterion of fever and grouping warrants further study. In summary, fever as a predictor of conversion from VTAS to thoracotomy in the management of empyema should be carefully evaluated, especially in the timing of fever. Within two days prior to surgery, fever neither decreased the successful rate of VATS in empyema, nor contributed to the prediction of the therapeutic outcome of empyema. The association of fever with empyema stage, pH and glucose in pleural effusion and pleural loculations on CT scan is observed in our study. Further study is needed to investigate the importance of fever as the most common symptom in empyema and the association between fever and peri-operative parameters in PPE patients.

Disclosure of conflict of interest

None.

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