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MAJOR ARTICLE

Culture-Positive and Culture-Negative Empyema After Thoracoscopic Decortication: A Comparison of Short-term and Long-term Outcomes

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Background. Empyema thoracis is a serious infectious disease and is associated with high morbidity and mortality. The perioperative outcomes between culture-positive and culture-negative empyema after thoracoscopic decortication remained controversial, especially since there were no studies that reported the survival outcomes between culture-positive and culture-negative empyema.

Methods. This single-institute study involved a retrospective analysis. Patients with empyema thoracis who underwent thoracoscopic decortication between January 2012 and December 2021 were included in the study. Patients were grouped into a culture-positive group and a culture-negative group according to culture results obtained no later than 2 weeks after surgery.

Results. A total of 1087 patients with empyema received surgery, and 824 were enrolled after exclusion. Among these, 366 patients showed positive culture results and 458 patients showed negative results. Longer intensive care unit stays (11.69 vs 5.64 days, $P < .001$), longer ventilator usage (24.70 vs 14.01 days, $P = .002$), and longer postoperative hospital stays (40.83 vs 28.37 days, $P < .001$) were observed in the culture-positive group. However, there was no significant difference in 30-day mortality between the 2 groups (5.2% in culture negative vs 5.0% in culture positive, $P = .913$). The 2-year survival was not significantly different between the 2 groups ($P = .236$).

Conclusions. Patients with culture-positive or culture-negative empyema who underwent thoracoscopic decortication showed similar short-term and long-term survival outcomes. A higher risk of death was associated with advanced age, a higher Charlson Comorbidity Index score, phase III empyema, and a cause other than pneumonia.

Keywords. culture; decortication; empyema; outcomes; survival.

Empyema thoracis is a serious infectious disease and is associated with high morbidity and mortality. It has been classified into 3 phases: (1) the exudative phase, (2) the fibrinopurulent phase, and (3) the organizing phase. Surgical intervention was recommended for phase II and phase III empyema [1]. Previous studies reported perioperative mortality rates from 3.1% to 9.5% [2–5].

Aside from surgical intervention, antibiotics are extremely vital in the treatment of empyema. However, the culture-positive rate is relatively low. Previous studies indicated that the positive rate of pleural fluid cultures only ranged from 19% to 49% and the relatively low positive-culture rate was due to previous antibiotic therapy [6, 7]. Our previous study reported that the combination of a pleural peels tissue culture and a pleural fluid culture could elevate the positive culture rate from 46.0% to 62.7% [8]. However, there were still many patients with empyema after surgery who remained culture negative. Thus, the selection of proper antibiotics can be difficult due to the bacteriology differing significantly among countries, regions, and even local hospitals [9]. Therefore, the use of broad-spectrum empirical intravenous antibiotics has been suggested once empyema is diagnosed [1].

The perioperative outcomes between culture-positive and culture-negative empyema after surgery remains controversial. Akamine et al suggested that culture-positive groups experienced shorter postoperative hospital stays and fewer complications [10]; another study held the opposite opinion [11]. There were seldom studies that discussed the long-term outcomes and survival between culture-positive and culture-negative empyema.

The aim of this study was to compare the outcomes between culture-positive empyema and culture-negative empyema. We also analyzed the treatment outcomes between different types

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of antibiotics used in patients with culture-negative empyema, in hopes of elucidating the optimal strategy of treatment for patients with culture-negative empyema after surgery.

METHODS

Patient Population and Selection

We conducted a single-center retrospective cohort study in our institute (Changhua Christian Hospital, Changhua, Taiwan). Adult patients aged >18 years who underwent thoracoscopic decortication between January 2012 and December 2021 were included. Follow-up was closed in April 2022. Patients who had recurrent empyema, an undetermined phase, missing culture data, or missing antibiotic data were excluded. Patients who used several antibiotics after operation were also excluded. The phase of empyema was identified by 2 doctors (Y.-F. Cheng and B.-Y. Wang) via a chest computed tomography image and intraoperative photos. This study was approved by the Institutional Review Board in our institution (IRB-221109), and informed consent from all participants was waived.

Patients were grouped into a culture-positive group and a culture-negative group according to culture results obtained no later than 2 weeks after surgery. The culture methods used included pleural peels tissue, pleural fluid, and blood cultures. Blood cultures were performed during admission or at the time of diagnosis. Both pleural peels tissue cultures and pleural fluid cultures were obtained during surgery. If 1 of the cultures showed a positive result, the patient was assigned to the culture-positive group; however, patients were grouped into the culture-negative group if all cultures showed negative results after 2 weeks. The antibiotic usage, both after diagnosis and after operation, was determined by infectious disease doctors based on the patient's infection history and vital signs. They checked the effectiveness of antibiotics twice a week by vital signs and laboratory data.

We analyzed patients' age, sex, smoking status, Charlson Comorbidity Index (CCI) score, phase, location, cause of empyema, laboratory data, pleural fluid data, and duration of preoperative antibiotic usage. The primary outcome measures for our study were overall survival rate and 30-day mortality rate after surgery. The secondary outcome measures included the durations of intensive care unit (ICU) stays, ventilator usage, and postoperative hospital stays. A patient was transferred to ward from ICU after weaning from ventilator and stabilization of vital signs. We also analyzed the usage of different types of antibiotics within the culture-negative group by comparing survival curves based on antibiotic usage.

Statistical Analyses

The culture-positive and culture-negative groups were compared using Wilcoxon rank-sum tests for continuous variables and χ^2 or Fisher exact tests for categorical variables. Survival curves were plotted by the Kaplan-Meier method. Univariate and multivariate analyses were performed with the Cox proportional hazards model. Covariates were selected based on clinical judgment. The following factors were included into analyses: culture result, age, sex, smoking status, CCI score, phase, location, cause, and preoperative antibiotic usage. All calculations were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corporation, Armonk, New York). P values $< .05$ were considered statistically significant.

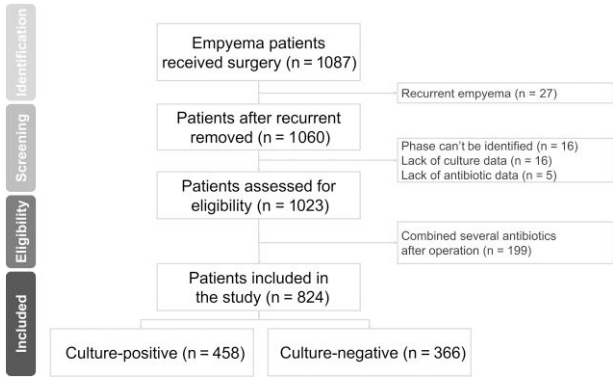

Figure 1. Flowchart of patient selection.

RESULTS

A total of 1087 patients with empyema underwent surgery, and 824 adults were enrolled after exclusion (Figure 1). Among those, 366 (44.4%) and 458 (55.6%) patients were assigned to the culture-negative empyema group and culture-positive empyema group, respectively. The basic data of the study patients were summarized in Table 1. The mean age was slightly older in the culture-positive group (61.14 vs 63.04 years, $P = .046$). Both groups were male predominant (77.3% in the negative group vs 80.6% in the positive group, $P = .255$). There was no significant difference in smoking status between the groups (68.3% vs 70.5% never smokers, $P = .492$).

More severe clinical statuses were noted in the culture-positive group regarding CCI score, phase of empyema, laboratory data, and pleural effusion data. The distributions of CCI scores for the culture-negative and culture-positive groups, respectively, were 24.3% and 18.8% for score 0, 34.2% and 30.6% for scores 1 and 2, and 41.5% and 50.7% for scores ≥3 ($P = .025$). Only 16.7% of culture-negative empyema cases were phase III compared to 24.7% of the culture-positive empyema cases ($P = .005$). The laboratory data indicated that the culture-positive group showed a higher absolute neutrophil count (ANC) than the culture-negative group (11 978 vs 10 754 cells/μL, $P = .008$). The pleural effusion data for the culture-negative (culture-positive) group revealed that 36.8%

Table 1. Basic Data of Patients With Empyema

Characteristic	Culture-Negative Empyema	Culture-Positive Empyema	*P* Value
No. of patients	366	458	
Age, y, mean ± SD	61.14 ± 15.68	63.04 ± 15.96	.046
Sex			.255
Male	283 (77.3)	369 (80.6)	
Female	83 (22.7)	89 (19.4)	
Smoking			.492
Never	250 (68.3)	323 (70.5)	
Ever	116 (31.7)	15 (29.5)	
CCI score			.025
0	89 (24.3)	86 (18.8)	
1–2	125 (34.2)	140 (30.6)	
≥3	152 (41.5)	232 (50.7)	
Phase			.005
II	305 (83.3)	345 (75.3)	
III	61 (16.7)	113 (24.7)	
Location			.560
Right	232 (63.4)	275 (60.0)	
Left	130 (35.5)	179 (39.1)	
Bilateral	4 (1.1)	4 (0.9)	
Cause			.405
Pneumonia	306 (83.6)	372 (81.2)	
From abdomen	11 (3.0)	15 (3.3)	
From neck/mediastinum	2 (0.5)	1 (0.2)	
Cancer related	28 (7.7)	27 (5.9)	
Iatrogenic	6 (1.6)	15 (3.3)	
Trauma	5 (1.4)	7 (1.5)	
From esophagus	2 (0.5)	5 (1.1)	
Others	6 (1.6)	16 (3.5)	
Laboratory data			
WBC count, cells/μL, mean ± SD	13 212.44 ± 5917.37	14 201.38 ± 7003.39	.081
ANC, cells/μL, mean ± SD	10 754.25 ± 5567.02	11 977.95 ± 6364.70	.008
Pleural effusion data			
pH ≤7.2	120 (36.8)	217 (54.3)	<.001
Glucose ≤40 mg/dL	89 (27.0)	187 (44.8)	<.001
LDH ≥1000 IU/L	166 (50.3)	267 (64.8)	<.001
Preoperative Abx usage, d, mean ± SD	5.91 ± 13.30	5.74 ± 15.03	.117
Bacteria empyema	…	385 (84.1)	
Fungal empyema	…	28 (6.1)	
Tuberculous empyema	…	45 (9.8)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: Abx, antibiotics; ANC, absolute neutrophil count; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; SD, standard deviation; WBC, white blood cell.

(54.3%) had a pH <7.2, 27.0% (44.8%) had a glucose level <40 mg/dL, and 50.3% (64.8%) had a lactate dehydrogenase (LDH) level >1000 IU/L. The average duration of preoperative antibiotic usage was 5.91 days in the culture-negative group and 5.74 days in the culture-positive group ($P = .117$). In the culture-negative empyema group, there were 385 (84.1%) patients with bacterial empyema, 28 (6.1%) patients with fungal empyema, and 45 (9.8%) patients with tuberculous empyema.

Table 2 shows the perioperative outcomes between culture-negative empyema and culture-positive empyema. Longer ICU stays (11.69 vs 5.64 days, $P < .001$), longer ventilator usage (24.70 vs 14.01 days, $P = .002$), and longer postoperative hospital stays (40.83 vs 28.37 days, $P < .001$) were observed in the culture-positive group. Most of the patients did not need a preoperative chest tube insertion or a postoperative ICU stay. The preoperative chest tube insertion rate and postoperative ICU stay rate were higher in the culture-positive group. However, there was no significant difference in 30-day mortality between the 2 groups (5.2% in culture negative vs 5.0% in culture positive, $P = .913$). The long-term outcomes were shown in Figure 2. There was no significant difference in 2-year survival between the 2 groups ($P = .236$).

The subgroup analysis is shown in Table 3. We analyzed the antibiotic usage for culture-negative empyema after operation.

Table 2. Outcomes of Surgery Between Culture-Negative and Culture-Positive Empyema

Outcome	Culture-Negative Empyema	Culture-Positive Empyema	*P* Value
ICU duration, d, mean ± SD	5.64 ± 25.58	11.69 ± 119.57	<.001
Ventilator duration, d, mean ± SD	14.01 ± 116.50	24.70 ± 177.23	.002
Hospital duration, d, mean ± SD	28.37 ± 116.06	40.83 ± 176.54	<.001
Preoperative chest tube duration, d, mean ± SD	2.69 ± 18.42	2.20 ± 6.35	.002
Preoperative chest tube insertion, No. (%)			
Yes	82 (22.4)	145 (31.7)	.003
No	284 (77.6)	313 (68.3)	
Postoperative ICU stay, No. (%)			
Yes	114 (31.1)	184 (40.2)	.007
No	252 (68.9)	274 (59.8)	
30-d mortality	19 (5.2)	23 (5.0)	.913

Abbreviations: ICU, intensive care unit; SD, standard deviation.

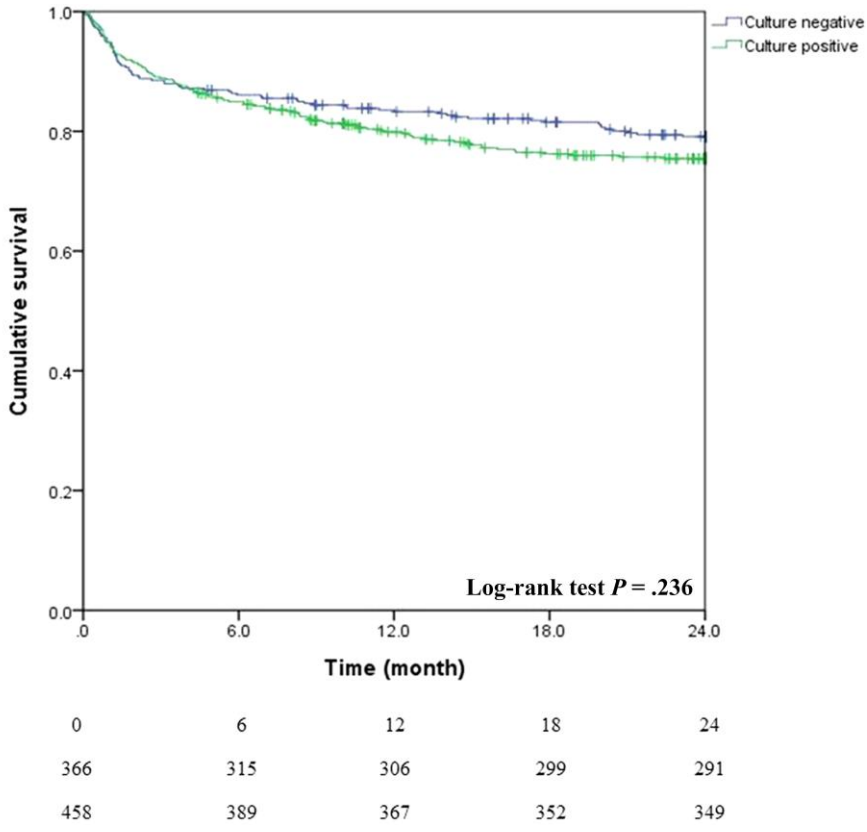

Figure 2. Kaplan-Meier survival curves of patients with culture-positive and culture-negative empyema.

The most commonly used antibiotics were ampicillin/sulbactam (41.3%) and piperacillin/tazobactam (18.0%). The long-term outcomes of patients with culture-negative empyema based on antibiotic usage are shown in Figure 3. The usage of piperacillin/tazobactam revealed the poorest survival curve. We further analyzed the basic data of 366 patients with culture-negative empyema in Table 4. We noticed that, compared to patients in other groups, the patients in the piperacillin/tazobactam group were older, had higher CCI scores and worse laboratory data, and were more likely to have phase III empyema.

Both the univariable and multivariable linear regression models for overall survival were analyzed in Table 5. Advanced age, higher CCI score, phase III empyema, right-sided empyema, cause other than pneumonia, and prolonged preoperative antibiotic usage were found to be statistically

associated with a worse survival in univariable analysis. In multivariable analysis, advanced age, higher CCI score, phase III empyema, and causes other than pneumonia were still significant factors.

DISCUSSION

In this study, we demonstrated that patients with culture-negative empyema had postoperative survival rates that were similar to those of patients with culture-positive empyema. Both groups had similar 30-day mortality rates and overall survival rates. To the best of our knowledge, this is the first study to compare postoperative survival between culture-positive and culture-negative empyema.

Table 3. Antibiotics Usage After Operation for Culture-Negative Empyema

Type of Antibiotic	Total Cohort, No. (%)
Ampicillin/sulbactam	151 (41.3)
Piperacillin/tazobactam	66 (18.0)
Flomoxef	27 (7.4)
Amoxicillin/clavulanate	25 (6.8)
Piperacillin	23 (6.3)
Ceftriaxone	19 (5.2)
Cefoxitin	14 (3.8)
Others	41 (11.2)

There were some studies that compared the perioperative morbidity between culture-positive and culture-negative empyema. Okiror et al enrolled 109 patients with stage III empyema who were operated on via the thoracotomy method, and they reported that culture-positive empyema was associated with a longer duration of pleural drainage, longer hospital stays, and more complications [11]. A prolonged course of intravenous antibiotics with at least 1 pleural drain left in situ for culture-positive empyema may explain these results. On the other hand, Akamine et al reported the results of 47 patients with stage II/III empyema who underwent surgery; they claimed that the hospital stays were shorter in the culture-positive group [10]. They speculated that culture-positive patients underwent early surgery, which could lead to early recovery and discharge from the hospital. However, both studies involved patient numbers on a small scale, treatment heterogeneity, and inconsistencies in the staging of empyema. Our study provided larger patient numbers and indicated that culture-positive empyema showed longer ICU stays, longer ventilator usage, and longer postoperative hospital stays, which opposes the hypothesis of Akamine et al. But in most situations, the diversity of patient clinical status, surgical intervention, and pathomorphology of empyema is not the same [12]. The treatment of empyema still remains flexible and individually tailored.

Our patients in the culture-positive group had worse basic conditions: older age, higher CCI scores, a higher proportion

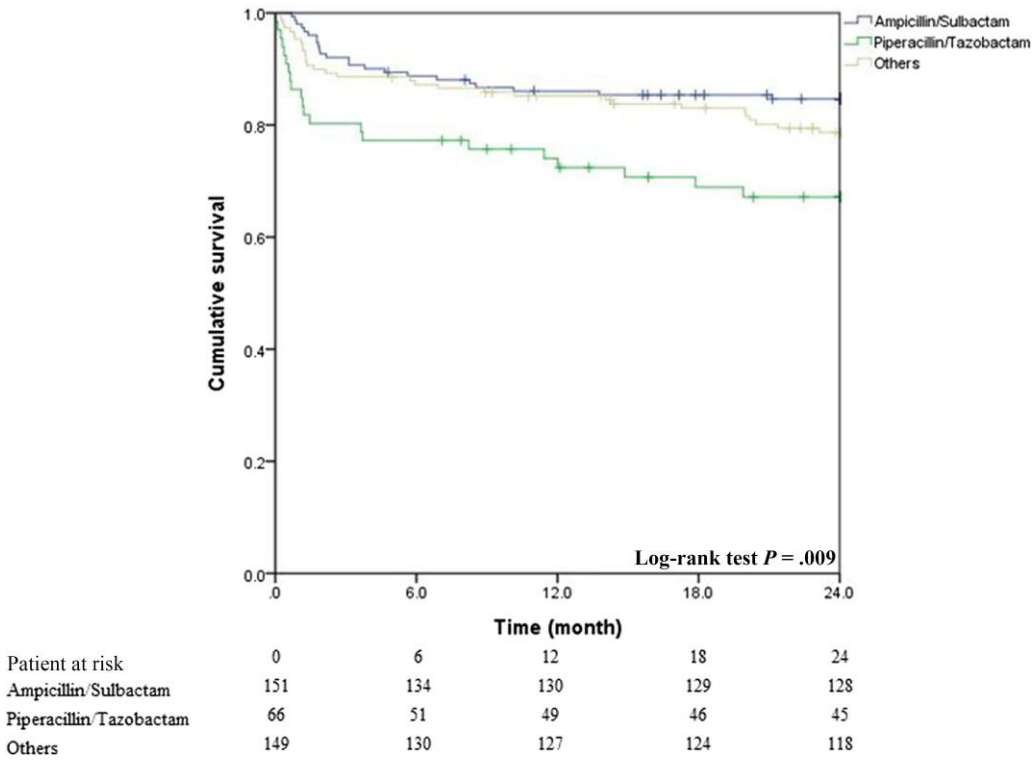

Figure 3. Kaplan-Meier survival curves of patients with culture-negative empyema receiving ampicillin/sulbactam, piperacillin/tazobactam, and other antibiotics.

Table 4. Basic Data of 366 Patients With Culture-Negative Empyema

Characteristic	Ampicillin/Sulbactam	Piperacillin/Tazobactam	Others	*P* Value
No. of patients	151	66	149	
Age, y, mean ± SD	60.82 ± 14.58	64.11 ± 13.65	60.15 ± 17.43	.267
Sex				
Male	126 (83.4)	49 (74.2)	108 (72.5)	.062
Female	25 (16.6)	17 (25.8)	41 (27.5)	
Smoking				
Never	98 (64.9)	49 (74.2)	103 (69.1)	.381
Ever	53 (35.1)	17 (25.8)	46 (30.9)	
CCI score				
0	40 (26.5)	15 (22.7)	34 (22.8)	.345
1–2	55 (36.4)	17 (25.8)	53 (35.6)	
≥3	56 (37.1)	34 (51.5)	62 (41.6)	
Phase				
II	129 (85.4)	53 (80.3)	123 (82.6)	.613
III	22 (14.6)	13 (19.7)	26 (17.4)	
Location				
Right	96 (63.6)	43 (65.2)	93 (62.4)	.358
Left	55 (36.4)	21 (31.8)	54 (36.2)	
Bilateral	0 (0.0)	2 (3.0)	2 (1.3)	
Cause				
Pneumonia	133 (88.1)	54 (81.8)	119 (79.9)	.088
From abdomen	0 (0.0)	2 (3.0)	9 (6.0)	
From neck/mediastinum	0 (0.0)	1 (1.5)	1 (0.7)	
Cancer related	10 (6.6)	6 (9.1)	12 (8.1)	
Iatrogenic	5 (3.3)	0 (0.0)	1 (0.7)	
Trauma	1 (0.7)	1 (1.5)	3 (2.0)	
From esophagus	0 (0.0)	0 (0.0)	2 (1.3)	
Others	2 (1.3)	2 (3.0)	2 (1.3)	
Laboratory data				
WBC count, cells/μL, mean ± SD	12 702.93 ± 5166.84	14 222.03 ± 6340.89	13 279.38 ± 6391.08	.233
ANC, cells/μL, mean ± SD	10 178.77 ± 4883.88	11 882.93 ± 5877.82	10 823.13 ± 5997.65	.112
Pleural effusion data				
pH ≤7.2	51 (38.1)	21 (37.5)	48 (35.3)	.889
Glucose ≤40 mg/dL	33 (24.1)	18 (32.1)	38 (27.7)	.502
LDH ≥1000 IU/L	71 (52.2)	30 (53.6)	65 (47.1)	.606
Preoperative Abx usage, d, mean ± SD	2.95 ± 3.42	5.08 ± 5.46	9.27 ± 19.76	<.001

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: Abx, antibiotics; ANC, absolute neutrophil count; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; SD, standard deviation; WBC, white blood cell.

of phase III cases, higher ANC, and worse pleural effusion data. In addition, there was some fungal and tuberculous empyema noted in the culture-positive group. Previous studies reported that fungal and tuberculous empyema provided poorer outcomes than bacterial empyema [13–15]. These might be the reasons why patients with culture-positive empyema needed longer ICU stays, longer ventilator usage, and longer postoperative hospital stays. However, the positive cultures might have helped us shift to specific antibiotic usage. In our point of view, the original poorer outcomes were corrected with the aid of correct antibiotic treatment. This might explain why culture-positive and culture-negative empyema resulted in similar long-term outcomes even though there were different basic conditions.

Regarding other infectious diseases, there were plenty of studies comparing the outcomes between culture-positive and culture-negative groups in the fields of infective endocarditis, osteomyelitis, periprosthetic joint infection, and sepsis. An analysis of 3113 patients with infective endocarditis indicated that a higher long-term mortality rate was observed in culture-negative patients compared with culture-positive patients [16]. Turning to osteomyelitis, a recent study revealed that the overall complication rate was much higher in the culture-positive group (32.0% vs 3.0%) [17]. In the field of periprosthetic joint infection, similar outcomes were noted between the culture-positive and culture-negative groups [18].

The outcomes of sepsis between culture-positive and culture-negative groups were well researched. Some studies supported that culture-positive sepsis led to longer hospitalizations and more morbidity and mortality [19–21]. However, most of the studies concluded that there was no short-term

Table 5. Univariate and Multivariate Analysis for Overall Survival

	Univariate		Multivariate	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Culture result				
Positive (ref)	1		1	
Negative	0.83 (.59–1.15)	.258	1.06 (.73–1.55)	.750
Age (per year)	1.03 (1.01–1.04)	<.001	1.02 (1.01–1.04)	.003
Sex				
Male (ref)	1		1	
Female	0.72 (.47–1.10)	.129	0.60 (.36–.99)	.046
Smoking				
Never (ref)	1		1	
Ever	1.00 (.70–1.43)	.993	0.88 (.57–1.36)	.563
CCI score				
0 (ref)	1		1	
1–2	2.84 (1.21–6.64)	.0163	2.37 (.99–5.66)	.052
≥3	15.22 (6.95–33.31)	<.001	10.81 (4.84–24.14)	<.001
Phase				
II (ref)	1		1	
III	2.08 (1.44–3.01)	<.001	1.88 (1.23–2.86)	.003
Location				
Right (ref)	1		1	
Left	0.64 (.45–.91)	.014	0.78 (.52–1.16)	.220
Bilateral	3.02 (.75–12.27)	.121	2.11 (.43–10.31)	.354
Cause				
Pneumonia (ref)	1		1	
Other	3.12 (2.13–4.57)	<.001	2.97 (1.91–4.60)	<.001
Preoperative Abx usage, d	1.02 (1.01–1.03)	.002	1.01 (1.00–1.02)	.061

Abbreviations: Abx, antibiotics; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.

or long-term survival difference between culture-positive and culture-negative sepsis [22–24].

In culture-negative empyema, the choice of antibiotics is challenging. The pathogen spectrum varies by country, region, and even hospital. Previous studies reported that *Streptococcus* species and anaerobes were in the majority of patients with community-acquired pneumonia and *Staphylococcus* species were in the majority of patients with hospital-acquired pneumonia [25, 26]. We tended to use broad-spectrum antibiotics to cover these pathogens when a patient was in a stable condition. For severely ill patients, antibiotics against methicillin-resistant *Staphylococcus aureus* and *Pseudomonas* species were chosen [1]. In this study, we tended to choose piperacillin/tazobactam for patients with culture-negative empyema with poorer basic conditions in order to cover a broad spectrum of pathogens. In fact, it was used more often in sicker patients regardless of whether the culture results were negative or positive. However, patients in this group still had worse outcomes.

A previous study also reported that antibiotic resistance may cause poor outcomes [27]. The antibiotic resistance could be predicted by patient clinical characteristics [9]. For instance, patients with cerebrovascular disease were related to infection from *Streptococcus milleri* and anaerobes while diabetes mellitus was associated with *Klebsiella* species [28]. This information could give us hints for the choice of antibiotics.

There are some limitations of our study. First, this retrospective study may contain a selection bias, which could affect the data analysis and outcomes. Second, a single-center study may reflect the condition and outcomes of a certain region while there are geographic variations in bacteriology. The results may differ among institutes. Furthermore, there was no standardized protocol for the choice of antibiotics for patients with culture-negative empyema. A prospective study is needed on the different kinds of antibiotics used on these patients. However, this study is the first study to report the short-term and long-term mortality rates of patients with culture-positive and culture-negative empyema after surgery. We believe that the treatment strategy may improve and survival outcomes will be better in the near future for this rare and fatal infectious disease.

Patients with culture-positive or culture-negative empyema who underwent surgery showed similar short-term and long-term survival outcomes. However, patients with culture-positive empyema had longer ICU stays, longer ventilator usage, and longer postoperative hospital stays. The risk of death was mostly associated with advanced age, higher CCI scores, phase III empyema, and causes other than pneumonia.

Notes

Patient consent. Written informed consent from all participants was waived by our instition. (Changhua Christian Hospital).

Potential conflicts of interest. The authors declare that they have no competing interests. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the views any governmental bodies or academic institutions.

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