JTD JOURNAL OF THORACIC DISEASE
A PEER-REVIEWED, OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN THORACIC DISEASES
IMPACT FACTOR 2.895

Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-21-1083

Reviewer A

Comment 1: Authors demonstrated the benefit of surgical approach in adults with empyema, but this study had some limits because of the nature of retrospective design. All patients enrolled into this study was from two centers. The clinical practice rule for management of empyema was totally different in this two centers. What makes the clinical practice difference between the two centers. Why not enrolled all patients with diagnosis of empyema and then divided into two groups, surgical or fibrinolytic approach?

Reply 1: We thank the reviewer for his comment. As well mentioned by the reviewer, the study reports the clinical/radiological and biological outcome of patients with PPE managed in two Thoracic Surgery University Centers with different approaches: one with an early surgical approach and the second with a fibrinolytic approach.
The two centers have established their management guidelines independently. However, both centers have now merged into a new center called the University Center of Thoracic Surgery of Western Switzerland. Given the close proximity of both centers (they are located only 45km away from each other), we can assume that the study population is similar from a demographic point of view, access to the hospital and type of infection. Thus, their management mostly differed in the Center habits/ guidelines for PPE. When fusing into one center, we realized we had different approaches and decided to study what impact these differences had on patient outcome. We totally agree with the reviewer that a study randomizing patients with empyema into fibrinolysis vs surgery should be performed and we are working on putting together this prospective randomized clinical trial. However, this retrospective study shows already that these approaches may have different outcomes on patients which justify further studying.

Changes 1: In the methods section, we now read:
lines 84-92 *"The Thoracic University Centers of Geneva and Lausanne are located 45 kilometers apart and have recently fused into one center: the Thoracic Surgery University Center of Western Switzerland. The management policies for PPE were different in each center while the study population can be considered similar given the*

geographical proximity, access to health care, infection microbiology and co-morbidity characteristics".

lines 91-94 *"All patients included in this study were judged operable (Karnofsky performance status score of 60 to 80 with no major cardiovascular co-morbidities) and diagnosed with PPE based on Chest CT, inflammation parameters in the bloodwork, pleural fluid contents (Light criteria, LDH, pH and Glucose) and pleural fluid cultures."*

Comment 2: There was no data mentioned about the pleural effusion study result. How could we confirm the diagnosis of empyema?

Response 2: We thank the reviewer for his comment. As mentioned in the method section (lines 96-97), the pleural fluid was characterized for each patient. However, we did not report this data. In the revised manuscript, we have added one extra table (Table 3) which reports the pleural fluid analysis (pH, Glucose, LDH) and microbiological culture results. We find that the pleural fluid characteristics were compatible with PPE and comparible between treatment groups. As reported by others in the past, pleural fluid cultures were positive in only 40% of patients with PPE.

Changes 2: We have added a table in the result section and discuss it. The revised result section now reads: **lines 168-170** "*The pleural fluid characteristics are reported in Table 3. Pleural fluid showed elevated levels of LDH, low glucose content and low pH in all patients which was compatible with PPE. Positive pleural fluid cultures were only observed in 40% of patients in both groups".*

Table 3:

Variable	Surgery	Fibrinolysis
pH	7.0 ± 0.4 [6.6-7.6]	6.9±0.6 [6.1-7.4]
Glucose (mmol/l)	2.0 ± 2.2 [0.1-6.6]	2.3 ± 2.4 [0.1-10.4]
LDH (U/L)	2269 ± 2339 [56-6487]	2231 ± 2674 [42;13206]
Germ identification	42.4%	35.5%
Enterobacteriaceae	0	6%
Oro-dental	12%	4%
Streptococcus	27%	16%
Staphilococcus	3%	4%

Pseudomonas	0	2%
Haemophilus	0	2%

Comment 3: There was no data mentioned about the underlying disease, such as COPD, D.M., CAD or liver cirrhosis.

Response 3: We thank the reviewer for his comment. As discussed in the methods section, all patients included in this study were judged operable based on their clinical evaluation or past medical exams. Therefore, patients with severe organ failure were not included. This is also likely the reason why none of the patients were hospitalized in the intensive care unit station. In the revised manuscript, we have added a table with patient co-morbidities that were available in 133 of 159 patients (83%)

Changes 3: We specify in the method section that the co-morbidities were recorded when available in 133 of 159 patients. In the result section, we also report the co-morbidity data and have added a table (table 2), **lines 166-168** *" The co-morbidities were mild, similar between both groups and did not affect patient operability (Table 2)"*

Table 2 : Patients co-morbidities

Co-morbidity	Surgery (N=66)*	Fibrinolysis (N=67) *	P-value
Systemic hypertension	22 (33.3%)	29 (43.3%)	0.248
Past history of ischemic cardiopathy	11 (16.7%)	7 (10.5%)	0.295
Past history of rhythmic cardiopathy	8 (12.1%)	8 (12.0%)	0.916
Chronic obstructive pulmonary bronchopathy	8 (12.1%)	7 (10.5%)	0.705
Diabetes mellitus	6 (9.1%)	14 (20.9%)	0.057
Nephropathy	5 (7.6%)	7 (10.5%)	0.563
Ethylism	12 (18.2%)	8 (11.9%)	0.314
Transient ischemic attack/stroke	0 (0%)	4 (6%)	0.119
Dementia	0 (0%)	4 (6%)	0.119
Oncological history	10 (15.1%)	12 (17.9%)	0.669

* Co-morbidities are available in 133 of 159 patients.

Comment 4: There was no data mentioned about the Intensive care unit stay. Was any patient also affected by respiratory failure, lung abscess or pneumonia?

Response 4: We thank the reviewer for his comment. As stated in response 3, patients had mild co-morbidities and were judged operable. None of them required intensive care unit management throughout their hospital stay. We have better specified this point in the result section which now reads on **lines 196-197**: *"and none of the patients required intensive care unit management during their entire hospital stay"*

Reviewer B

General comments

The authors reported that surgical management of VATS for parapneumonic empyema (PPE) was associated with shorter duration of chest tube insertion and length of hospital stay and better pleural space control on the X-ray compared with intrapleural administration of fibrinolytic agent.

This report is a retrospective study of cases between two centers by treatment modality. It is a useful report for respiratory surgeons because it shows the results of two clinically selective treatment methods.

However, I have some concerns that should be addressed regarding the report contents.

Specific comments

a) Major

Comment 1: The mean age of the "Fibrinolysis" group was 6 years older than the "Surgery" group. This may have affected the choice of treatment and the outcome of the treatment. Please discuss this point in your discussion.

Response 1:

We thank the reviewer for his comment. We agree that the patients managed surgically in our study were, on average, 6 years older than the patients managed by fibrinolysis. However, as stipulated in the methods and result section, all patients included in this study were judged operable. In addition, none of the patients required intensive care unit management and, in the fibrinolytic group, when treatment failed, patients underwent surgery.

Our study remains retrospective with its limitations. We discuss the age difference in

our discussion section but stipulate that the Karnofsky score of all patients was located between 60 and 80. To be able to address this issue, a prospective randomized trial is mandatory.

Changes 1: The discussion section now reads **lines 220-223**: *"We did find a significant difference in the mean age of patients between (6 years younger in the surgery group) between treatments. While patients were all judged operable, it is possible that more advanced ages in the fibrinolytic group may have affected decision to undergo surgery in case of partial lung re-expansion. However, this did not affect infection control outcome".*
In the revised manuscript, we now also report patient co-morbidities which are similar between groups (Table 2)

b) Minor

Comment 1: Please unify the abbreviations of PPE; Parapneumonic pleural effusion (PPE) or Parapneumonic empyema (PPE) have different meanings.

Response 1: We thank the reviewer for his comment and have made the appropriate changes throughout the text. All abbreviations have been changed as Parapneumonic Empyema (PPE)

Changes 1: Performed throughout the text

Comment 2: The duration between the start of initial drainage for the PPE and the start of surgery or fibrinolytic therapy should be indicated.

Response 2: We thank the reviewer for his comment. Regarding the time between drainage and initiation of fibrinolytic therapy, there was no delay. Fibrinolysis was started at time of drain placement. Regarding the time between initial drainage and surgery, the latter was of 2±2 days [0 to 6 day]. We have relatively easy access to the OR for differed emergencies which explains this very short time reported.

Changes 2: In the result section, we specify this point: **lines 170-171** "*Surgery was performed by VATS in all cases within 2±2 days [0-6days] following patient drainage while fibrinolysis was initiated at time of drainage*". Also, in the discussion section we discuss the ease of access to OR: **lines 264-269**: "*Two additional factors may have affected patient stay: the time between initial drainage and surgical management and the social, general state or rehabilitation requirement of patients. In the surgical*

hospital, access to the OR for differed emergencies was possible within a very short timeframe. This may not be the case in other hospital structures. Regarding the delayed discharge in patients who have completed the treatment, there are more reasons such as the general state of the patient, social factors and rehabilitation requirement".

Comment 3: For some variables, a range should be added in addition to the mean ± SD to show the full range of values. Age, white blood cell count, CRP, pleural effusion area changes at day 7 (%).

Response 3: We thank the reviewer for his comment and have added the range to all appropriate locations

Changes 3: Updated tables 1 and 2.

Table 1: Patient characteristics

	Surgery	**Fibrinolysis**	
Variable	**N=66**	**N=93**	**P-value**
Age (years), mean+/-SD [range]	**56±16 [17-84]**	**62±17 [23-94]**	**0.048**
Gender (male, %)	46 (69.7)	64 (68.8)	0.906
Side (right, %)	38 (57.6)	56 (60.2)	0.739
Leukocytes day 0 (G/l), mean+/-SD [range]	**18.2±8.6 [6-48]**	**14.9±6.4 [5-45]**	**0.006**
CRP day 0 (mg/l), mean+/-SD [range]	202.8±125.2 [18-532]	205.2±106.8 [16-478]	0.895
Germ identification (%)	28 (42.4)	33 (35.5)	0.375

Table 2: Clinical outcome

	Surgery	**Fibrinolysis**	
Variable	**N=66**	**N=93**	**P-value**
Pleural effusion area changes at day7 (%), mean+/-SD [range]	**-22 ±18 [-80-6]**	**-16±17 [-71-12]**	**0.035**
Additional drain (%)	**3 (4.6)**	**20 (21.5)**	**0.003**

Referral to surgery or redo (%)	**2 (3)**	**12 (12.9)**	**0.03**
Hemothorax (%)	2 (3.1)	0 (0)	0.17
Arrhythmia (%)	**4 (6.1)**	**0 (0)**	**0.027**
Drainage duration, median [IQR]	**3 [2 – 4]**	**5 [4-7]**	**<0.0001**
Hospital length of stay, median [IQR]	**7 [5 – 10]**	**11 [7-19]**	**<0.0001**

Comment 4: The average observation period after discharge from the hospital should be indicated. If possible, please indicate the mortality rate for 90 days and 1 year after the treatment intervention as well as the 30-day mortality. The rate of recurrence of empyema and the rate of rehospitalization should also be shown in order to assess the effectiveness of the treatment.

Response 4: We thank the reviewer for his comment. We unfortunately did not have data available for 90 day mortality or 360 day mortality. However, during the 30-day post-therapy period, no patient was re-admitted or recurred an infection/effusion.

Changes 4: This point is discussed in the discussion section **lines 259-262**: "*We had patient data up to 30 days after their discharge and did not observe recurrences, re-hospitalizations within this period. However, longer term assessements at 90 days and 1 year would be of interest regarding general activities, empyema recurrence and mortality".*

Comment 5: Indicate the severity of the arrhythmia. For example, if the arrhythmia requires surgical or therapeutic intervention, please indicate the severity according to the Cavien-Dindo classification or common terminology criteria for adverse events (CTCAE).

Response 5: We thank the reviewer for his comment. We only observed 4 cases of the surgery group that developed arrhythmia. The latter all consisted in Grade 2 complications based on the Clavien-Dindo classification that were all managed by amiodarone therapy that was introduced and maintained for a duration of 3 months.

Changes 5: We have specified in the results section the degree of arrhythmia complication. It now reads on **lines 186-187**: *"The latter were all treated pharmacologically and consisted in Grade 2 complications according to the Clavien Dindo classification".*

Comment 6: Please show the results of the surgery and the fibrinolytic treatment.

6-1: For example, in the "Surgery" group, please describe the operation time, blood loss, number of ports, anesthesia method, and postoperative complications (frequency of postoperative pulmonary fistula, postoperative respiratory failure, pneumonia, etc.).
6-2: In the "Fibrinolysis" group, 9 patients suffered from "hematic chest tube output". Please clarify the fibrinolytic agent used in these cases, the time from the start of administration to bleeding, and the treatment required to stop bleeding.

Response 6:
6-1: We thank the reviewer for his comment. In the "Surgery" group, we recorded a mean operation time of 122±55 minutes with a range of [27-255 minutes]. The surgical approach consisted in a 3 port anterior approach with patients placed on general anesthesia with a double lumen tube. A first step consisted in lung liberation from the chest wall, the mediastinum and the diaphragm followed by pleural decortication. For this particular step, a CPAP device was placed on the excluded lung with a pressure of 5 to 10cm of water to facilitate lung decortication. We did not used epidural analgesia. In the postoperative course, 4 patients developed persistant air leak (more than 7 days) that were managed by Heimlich valves and chest tube ablation after 15 days, 2 patients developed a hemothorax that required surgical evacuation (Complication Grade IIIB according to Clavien Dindo) and 4 patients developed arrhythmia (Complication Grade II according to Clavien Dindo). All patients were treated with wide range antibiotics for pneumonia and did not require antibiotherapy changes because of uncontrolled infection. Instead, some had antibiotic restriction based on cultured germs.

6.2: In the Fibrinolysis group, 9 patients developed hematic chest tube output following pharmacological instillation of TPa-DNAse in all 9 cases. This complication was managed by stopping the fibrinolysis instillation and observing the chest X-ray to ensure no hematoma accumulated in the pleural space. In all cases, this complication could be managed conservatively.

Changes 6:

6.1: We have better specified the surgical approach in the methods section which now reads **lines 107-114:** "*The surgical approach consisted in a 3 port anterior approach with patients placed on general anesthesia with a double lumen tube. A first step consisted in lung liberation from the chest wall, the mediastinum and the diaphragm followed by pleural decortication. For this particular step, a CPAP device was placed on the excluded lung with a pressure of 5 to 10cm of water to facilitate lung*

decortication. The lung was cleared from all fibrous tissue, pus and septa, the fissures were open, the diaphragm was freed and the obliteration of the space by the decorticated lung was checked for all cases. We did not used epidural analgesia"

And have added some results in the result section which now reads **lines 185-199:** "*Arrhythmia was, on the contrary, more frequent in the surgical group (6.1% vs 0%, P=0.027 in the surgical and fibrinolytic group respectively). The latter were all treated pharmacologically (Clavien Dindo Grade II complication). A highly hematic chest tube output occurred in 9 patients of the fibrinolytic group (9.6%) which was successfully managed by treatment interruption. Referral to surgery was required in 12 patients of the fibrinolytic group (12.9%) and could be performed by VATS in all cases. Two patients (3%) of the surgical group required re-operation to manage a postoperative hemothorax (Clavien Dindo Grade IIIB complication). Finally, 4 patients from the surgical group developed persistent air leak (more than 7 days) that were managed by Heimlich Valve placement and where chest tubes could all be removed by postoperative day 15 (Clavien Dindo Grade I complication). There was no 30-day mortality and none of the patients required intensive care unit management during their entire hospital stay".*

6-2: the result section now reads **lines 188-191:** "*All patients with this complication had been treated by TPa-DNAse fibrinolysis and were successfully managed by treatment interruption and chest X-ray observation. No additional treatment was required for this complication (Clavien Dindo Grade I)*".

Comment 7: Evaluation of pleural effusion by X-ray is affected by the position of the patient at the time of imaging, please clarify the regulations.

Response 7: We thank the reviewer for his comment. We agree with the reviewer that the positioning of the patient is mandatory for X-ray comparison. In all cases, the X-rays were performed in the upright standing or sitting position. No X-ray reported in this study was performed in bed with a lying patient. Therefore, the findings are comparible between groups.

Changes 7: We have better specified this particular point the the methods section which now reads: **lines 136-137**" *All chest X-rays used for this part of the study were performed on patients either standing up or sitting in the upright position (no X-rays in bed with lying patients)*".

Comment 8: Identify the proportion of ATS-2 and ATS-3 in the PPE of the patients.

Response 8: We thank the reviewer for his comment. To our knowledge, ATS classification can only be reported accurately in case of a surgical intervention which signs the fibrinopurulent or organized stages with certitude. We have checked this particular parameter in our database. Of the 66 surgical patients, 42 (63.6%) had ATS-2 and 24 (36.4) ATS-3 PPEs. Given the population between both centers was geographically close, we assume the ATS levels of PPE were comparible between Surgical and Fibrinolytic groups.

Changes 8: We have added in the result section **lines 175-177**: *"The ATS PPE classification could be accurately determined in the 66 patients of the surgical group with 42 patients (63.6%) that had ATS-2 and 24 patients (36.4%) that had ATS-3 PPE".*

Comment 9: For "Germ identification", please write the name of the main organism.

Response 9: We thank the reviewer for his comment. As asked by Reviewer 1, we have added a table (Table 3) with all pleural germ identification data.

Changes 9:

Table 3:

Variable	Surgery	Fibrinolysis
pH	7.0 ± 0.4 [6.6-7.6]	6.9±0.6 [6.1-7.4]
Glucose (mmol/l)	2.0 ± 2.2 [0.1-6.6]	2.3 ± 2.4 [0.1-10.4]
LDH (U/L)	2269 ± 2339 [56-6487]	2231 ± 2674 [42;13206]
Germ identification	42.4%	35.5%
Enterobacteriaceae	0	6%
Oro-dental	12%	4%
Streptococcus	27%	16%
Staphilococcus	3%	4%
Pseudomonas	0	2%
Haemophilus	0	2%

Reviewer C

Good report

Prospective randomized trial would be helpful

We agree with the reviewer's comment.

Response C: We thank the reviewer for his comment.