Video-Assisted Thoracoscopic Surgery of Parapneumonic Empyema – a 10-year Single-Centre Experience

Management parapneumonischer Empyeme per VATS – 10 Jahre Erfahrung eines Thoraxzentrums

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ABSTRACT

Objectives Evaluation of a standardised management for the treatment of patients with parapneumonic empyema. **Methods** A retrospective 10-year single-centre analysis of all patients with parapneumonic empyema undergoing a standardised thoracoscopic treatment approach. We describe referral and age patterns, microbiological results,

overall and stage-dependent success rates, conversion rates, 30-day and in-hospital mortality.

Results From May 2003 to April 2013, 248 patients with parapneumonic empyemas were treated in our centre. Most patients were referred at weekends, and younger patients had advanced stages. The cure rate in stage I was 97.6% and reached 80.3% in stage II and 63.1% in stage III. 6 patients (2.4%) (all stage III) needed conversion to an open procedure. A revision was required in 19.7% of cases

in stage II and 27.7% in stage III. 30-day mortality was 4.8%, in-hospital mortality was 8.1%.

Conclusion A standardised approach, including VATS, is associated with a high cure, low revision and moderate conversion rates. In view of a still considerable mortality, a higher index of suspicion and detection of advanced stages, especially in younger patients, is required to improve outcomes.

ZUSAMMENFASSUNG

Ziel der Studie Auswertung einer standardisierten Behandlungsstrategie für Patienten mit parapneumonischen Empyemen.

Methoden Retrospektive Analyse von 248 Patienten mit einem parapneumonischen Empyem während eines 10-Jahres-Zeitraumes in einem Thoraxzentrum.

Ergebnisse Von Mai 2003 bis April 2013 wurden insgesamt 248 Patienten mit parapneumonischen Empyemen operativ versorgt. Die meisten Patienten wurden an Wochenenden, speziell freitags, aufgenommen, und jüngere Patienten wiesen fortgeschrittene Stadien auf. Im Stadium I betrug die Erfolgsquote 97,6%, im Stadium II 80,3% und im Stadium III 63,1%. Bei 6 Patienten (2,4%) in Stadium III war eine Konversion auf ein offenes Vorgehen erforderlich. Eine Revision erfolgte bei 19,7% aller Fälle im Stadium II und in 27,7% der Fälle im Stadium III. Die 30-Tage-Letalität betrug 4,8%, die Krankenhaus-Letalität 8,1%.

Schlussfolgerungen Ein standardisiertes Vorgehen durch VATS ist verbunden mit einer hohen Erfolgsquote und einer niedrigen Konversions- und moderaten Revisionsrate. Angesichts einer erheblichen Letalität ist eine frühere Diagnostik zur Verbesserung der Ergebnisse erforderlich, insbesondere bei jüngeren Patienten.

Introduction

Pleural empyema continues to be a serious condition associated with considerable morbidity and hospital mortality. The etiology is heterogeneous, pneumonia being the most frequent cause, representing 40-60% of all pleural empyemas [1]. The

optimal treatment strategy is still a matter of debate, in particular as regards the role of VATS.

There are only few randomised controlled trails available, and there have been conflicting results. Not surprising, the recommendations of the British Thoracic Society and the American College of Chest Physicans vary in several issues [2, 3]. In this study, we describe the outcome of a cohort of patients with parapneumonic empyemas treated with a VATS-approach with regard to initial success, conversion rate, revision operations, duration of hospitalisation and survival. In addition, we analyze the impact of age and antibiotic treatment duration on intraoperative stage, as well as predictors of duration of hospitalisation and mortality.

Patients and methods

Population

From May 2003 to April 2013, 479 patients with 518 pleural empyemas were treated in our centre. Overall, 278 were of parapneumonic origin (248 primary and 30 parapneumonic recurrences). Non-parapneumonic pleural empyemas (n = 240) as well as the 30 recurrences were excluded from the study. Furthermore, we excluded all patients with severe immunosuppression.

Diagnostic approach

The diagnostic approach in our centre included a contrast-enhanced computed tomography of the thorax in all patients presenting with pleural effusion in the course of pneumonia, and who met the following criteria: body temperature >38 °C, C-reactive protein \ge 95 nmol/L and leukocyte count \ge 10 * 10⁹/L. Radiological signs suspicious of an empyema were: pleural thickening, pleural contrast enhancement, pleural fluids Hounsfield units about 30 and the spatial aspect of the liquid distribution. Empyema was confirmed by a diagnostic pleurocentesis (frank pus, and/or pH <7.0). Blood cultures were taken in case of suspicion of sepsis at admission.

Antimicrobial therapy

In patients without apparent infiltrates at CT, a preexisting antimicrobial therapy was discontinued postoperatively. If pneumonic infiltrates were present in pre-surgical CT or after VATS, antimicrobial therapy was started or continued.

Operative strategy

All patients were subjected to VATS and treated by 1 of 6 surgeons from a team of specialists in thoracic surgery, and by a standardised procedure. Confirmed empyemas were classified, according to the classification of the American Thoracic Society (ATS) [4].

After double-lumen tube intubation, surgery was performed in a lateral decubitus position under general anesthesia. Preoperatively, a flexible video bronchoscopy was performed, and tracheobronchial secretions were sampled for microbiological diagnostics. Primary approach was in the 5th intercostal space in the anterior axillary line. Additional trocars were placed under visual or palpatory control in the 8th intercostal space in the posterior axillary line and the 7th intercostal space. In some cases, 4 approaches were required. Intrathoracic conditions/radiologic or sonographic findings were always considered for the exact positioning of the primary approach. This was followed by a camera change into the 8th intercostal space. Pleural adhesions were detached carefully. An intrathoracic After complete mobilisation of the lung, debridement of the entire thoracic cavity and decortication of the visceral pleura, the pleural cavity was rinsed with 1000 ml Octenidindihydrochlorid-solution as an antiseptic and subsequently rinsed with 1000 ml RINGER®-solution. Finally, a 28 Ch 90° curved thoracic drainage was placed in dorso-basal region. In addition, a 28 Ch straight chest tube was placed anterior-apical. In some cases, the introduction of a third 28 Ch straight chest drainage was required dorsal-apical. Full expansion of the lungs as well as correct placement of the chest tube were documented by chest radiography promptly postoperatively.

The drainages were connected to a closed drainage system (Pleur-Evac[®] Sahara from Teleflex (Ireland)) and a suction of 50 cm H2O via a tube system was applied; alternatively, a digital drainage system (Topaz[®] from Medela (Switzerland)) with the same suction was used.

In order to prevent pleural adherence, an instillation of Streptokinase[®] (250.000 U in 50 ml NaCl) or Urokinase[®] (100.000 U in 50 ml NaCl) via the placed chest tubes was performed in the first 3 days postoperatively. After an exposure time of 2 hours, a rinsing with 1000 ml RINGER-solution followed. From the 4th to the 6th postoperative day we proceeded with a daily discontinuous rinsing with 1000 ml RINGER-solution. Samples of drainage fluid for microbiologic examination were taken before rinsing on 2 consecutive days and rinsing was subsequently continued. Chest tubes were removed if the samples proved microbiologically inconspicuous. In case of persisting or altered pathogens, chest tubes were exchanged under sterile conditions in local anesthesia and rinsing was continued for further 5 days. Afterwards, drainage samples were again collected on 2 consecutive days under sterile conditions. This procedure was repeated until all samples proved microbiological negative.

To open the atelectasis after surgery we applied a SALVIA[®] as oscillating positive pressure device and the Voldyne[®] as incentive spirometer. In addition, we applied inhalation therapy and each patient received respiratory therapy from a physiotherapist, both individually and in a group.

Variables

The following variables were recorded: age, sex, relevant comorbidities (and their number), stage of empyema according to ATS classification, microbiological findings in respiratory secretions, pleural fluid and blood cultures, presence and preoperative duration of antimicrobial therapy, surgical results (conversion rates, revision operations, duration of hospitalisation, survival and the need of rinsing therapy after discharge).

Treatment duration (length of treatment, LOT) was defined as time from chest tube insertion or VATS until the end of drainage. Length of hospitalisation (LOH) was the time from admission to discharge or death.

Mortality was recorded as 30-day and in-hospital mortality.

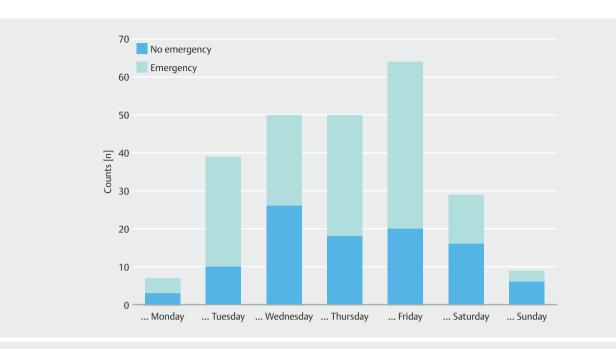


Fig. 1 Referral pattern to our centre according to weekdays.

Statistics

Excel 2010 was used for data collection and SPSS 19.0 for data analysis.

Means were compared by student's t-test, and categorical variables by chi-square test or Fisher's exact test in case of small expected frequencies. The level of significance was set at 5%.

Results

Clinical characteristics

From May 2003 to April 2013, overall 248 patients (66.9% male, 33.1% female) were treated with parapneumonic empyema at our institution. Median age was 58 years (range 12-92). 64.1% were younger than 65 years

Pleural empyema was the admission diagnosis in 206 patients (83.1%). The remaining 42 patients (16.9%) were referred to our centre with other diagnoses and empyema was diagnosed intraoperatively.

Referral to our centre was lowest on saturdays, sundays and mondays, and highest on fridays. 149 patients required urgent therapy, with a striking maximum of 44 patients also on fridays (**> Fig.1**).

41 patients (16.5%) were classified as stage I, 142 (57.3%) as stage II and 65 (26.2%) as stage III according to ATS. The right side was affected in 146 cases (58.9%) and the left side in 102 cases (41.1%). \blacktriangleright Fig.2 shows the distribution of age in each stage. Advanced stages were more frequent in younger ages and vice versa.

The frequency and type of comorbidities is summarised in **Table 1**. 73 patients (29.4%) had 1 comorbidity and 112 patients (45.2%) 2 or more comorbidities; 63 patients (25.4%) **Table 1** Frequency and types of comorbidities.

Comorbidity	Frequency		
Cardiac disease	67	(27,0%)	
Respiratory disease	50	(20,2%)	
Liver disease	12	(4,8%)	
Kidney disease	35	(14,1%)	
Tumor (extrapulmonary)	29	(11,7%)	
Alcohol/drug abuse	31	(12,5%)	
Diabetes mellitus	44	(17,7%)	
Neurologic disease	37	(14,9%)	
Vascular disease	13	(5,2%)	
Chronic Infections	23	(9,3%)	

had no comorbidity. Cardiac and pulmonary conditions were the most frequent comorbidities.

Microbiological results

Microbiological findings of initial investigations are listed in ► Table 2. A pathogen could be identified from bronchial fluid in 35.5%, from intrathoracic samples (i. e. pleural fluids as well as tissue homogenates) in 41.1% and from blood culture in 5.2% of patients. There was a broad spectrum of isolates, with enterobacteriaceae and nonfermenters being the most frequent isolates in bronchial secretions and anaerobes, followed by viridans streptococci in pleural fluid. In contrast, S. pneumoniae was the most frequent pathogen in blood cultures.

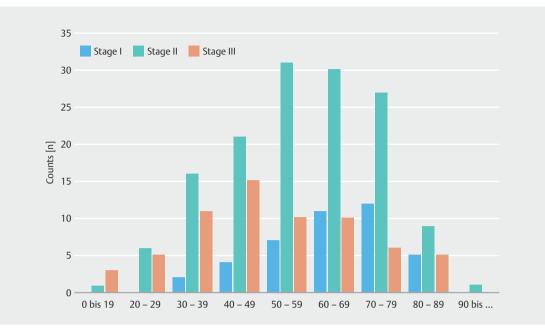


Fig.2 Distribution of ages according to ATS staging of parapneumonic empyema.

Pathogens	Bronchial secretions n/%		Pleural fluid n/%		Blood culture n/%	
Streptococcus (β-hemolytic)	7	5.7	10	7.0	0	-
Streptococcus (viridans-group) ¹	6	4.9	24	16.8	1	3.8
Streptococcus pneumoniae	9	7.3	10	7.0	7	26.9
Staph. aureus (MSSA)	10	8.1	2	1.4	2	7.7
Staph. aureus (MRSA)	10	8.1	6	4.2	1	3.8
Coagnegative staphylococci	1	0.8	13	9.1	6	23.1
Enterococcus spp.	1	0.8	3	2.1	1	3.8
Haemophilus influenzae	6	4.9	1	0.7	0	-
Moraxella catarrhalis	0	-	0	-	0	-
Enterobacteriaceae ²	34	27.6	14	9.8	4	15.4
Salmonella spp.	0	-	2	1.4	0	-
Nonfermenters ³	13	10.6	3	2.1	0	-
Legionella spp.	1	0.8	0	-	0	-
Anaerobes ⁴	2	1.6	39	27.3	2	7.7
Candida spp.	21	17.1	3	2.1	0	-
Others	2	1.6	13	9.1	2	7.7
Total	123	100	143	100	26	100

Table 2 Microbiological results in bronchial secretions, pleural fluid and blood cultures.

¹ Streptococcus anginosus, constellatus, intermedius, milleri, oralis, salivarius, sanguinis, vestibularis

² Citrobacter spp., Eikenella spp., Enterobacter spp., Escherischia coli, Hafnia alvei, Klebsiella spp., Morganella morganii, Proteus spp., Providentia spp., Serratia spp.

³ Acinetobacter spp., Pseudomonas aeruginosa, Stenotrophomonas maltophilia ⁴ Bacteroides spp., Clostridium spp., Fusobacterium spp., Peptostreptococcus spp., Porphyromonas spp., Prevotella spp., Propionibacterium spp., Veillonella spp.

	Stage I	Stage II	Stage III
n [%]	41 (16.5%)	142 (57.3%)	65 (26.2%)
Length of hospitalisation (LOH) [median, days]	10	16	15
Length ot treatment (LOT) [median, days]	7	13	13
Conversion [n]	0	0	6 (9.2%)
Revision [n]	0	28 (19.7%)	18 (27.7%)
Cure, [n] (%)	40 (97.6%)	114 (80.3%)	41 (63.1%)
30-day mortality [n] (%)	2 (4.9%)	9 (6.3%)	1 (1.5%)
In-hospital deaths [n] (%)	1 (2.4%)	16 (11.3%)	3 (4.6%)

Antimicrobial therapy

Antimicrobial therapy prior to thoracic surgical treatment was administered to 223 patients (89.9%). At referral, 90% of patients at stage I were treated, 89% at stage II and 91% at stage III. Postoperative antimicrobial treatment was administered in 56% of patients at stage I, 55% at stage II and 42% at stage III.

Surgical Results

Overall results of surgical therapy

Surgical treatment was usually performed on the day of admission. In 4 hemodynamically unstable patients (1.6%) video-assisted thoracoscopic surgery (VATS) was performed after hemodynamic stabilisation. 1 of these patients died, so a total of 247 patients (99.6%) were treated by VATS.

A conversion to thoracotomy was necessary in 6 patients (2.4%) (all stage III).

195 patients (78.6%) treated by VATS recovered without complications. In contrast, 46 patients (18.5%) required a revision, of these 10 patients (4.0%) due to postoperative hemothorax, 35 patients (14.1%) due to persistent infection and 1 patient (0.4%) due to persistent postoperative air leakage. We did not register any side effects that could be attributed to the use of Octenidindihydrochlorid-solution.

Of the 35 patients revised due to a persistent infection, the second intervention resulted in full recovery in 24 patients (68.6%), 11 patients (31.4%) required further revisions. In 6 patients (2.4%) (5 stage II and 1 patient stage III) the installation of a thoracostoma was necessary; a closure of the thoracostoma was possible in all these patients during follow-up.

The mean length of treatment (LOT) was 17.8 days \pm 18.2 days [median: 12 days, range 0–124]. Overall, 20 patients (8.1%) died during hospitalisation. Of these, 12 patients (4.8%) died postoperatively within a period of 30 days. 1 patient (0.4%) died after installation of a chest tube and before VATS. Causes of death remained undetermined in most cases except sepsis (n=2) and pulmonary embolism (n=1).

Results of surgical therapy according to stage of empyema

The results according to stage of empyema are summarised in **Table 3**.

Stage I

41 patients (16.5%) presented at stage I. The mean length of hospitalisation (LOH) was 11 days \pm 5.8 days [median: 10 days, range 5–35], whereas the mean length of treatment (LOT) was 8 days \pm 3.7 days [median: 7 days, range: 3–20].

38 patients (92.7%) underwent primary surgery by VATS with an average length of treatment (LOT) of 8 days \pm 3.6 days [median: 6 days, range 3–20].

3 unstable patients were initially supplied with a chest tube prior to VATS. 1 of these patients (2.4% based on the subgroup) died, the others received a video-assisted thoracoscopic surgery (VATS) after stabilisation. The mean length of treatment (LOT) of these patients was 13 days \pm 1.0 days [median: 13 days, range 12–14].

Stage II

Stage II was diagnosed in 142 patients (57.3%). The average length of hospitalisation (LOH) was 25 days \pm 26.4 days [median: 16 days, range: 0–168] and the mean length of treatment (LOT) was 21 days \pm 21.21 days [median: 13 days, range: 0–124].

141 patients (99.3%) underwent primary surgery by VATS. Again, 1 hemodynamically unstable patient had a delay prior to VATS. A primary cure could be achieved in 114 patients (80.3%). Of these, the mean length of hospitalisation (LOH) was 18 days \pm 10.3 days [median: 15 days, range 0–68]. The mean length of treatment (LOT) was 14 days \pm 9.0 days [median: 12 days, 0–60].

A total of 28 patients (19.7%) had to be revised. In this group, the mean length of treatment (LOT) extended to 48 days \pm 31.9 days [median: 44 days, 6–124]. In 13 patients (9.2%) postoperative lavage had to be continued on an outpatient basis after discharge from hospital.

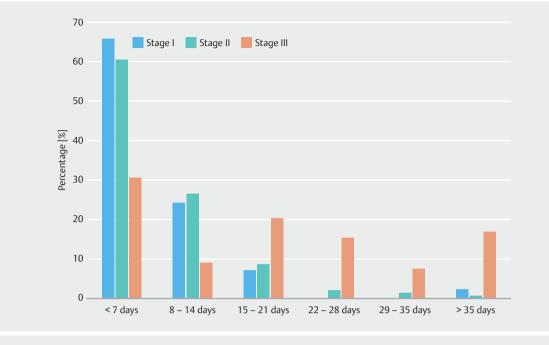


Fig.3 Duration of antibiotic therapy compared by stage of empyema.

Stage III

Stage III was diagnosed in 65 patients (26.2%) with a mean length of hospitalisation (LOH) of 20 days \pm 14.8 days [median: 15 days, range 0–76]. The mean length of treatment (LOT) was 18 days \pm 14.1 days [median: 13 days, range 0–69].

All patients were operated primarily by VATS, a conversion to thoracotomy was required in 6 patients (9.2%).

Primary cure was achieved in 41 patients (63.1%). In this group, the mean length of treatment (LOT) was 13 days \pm 7.4 days [median: 11 days, range 0–39].

In 18 patients (27.7%), surgical revision was necessary. In this subgroup, the mean length of treatment (LOT) extended to 27 days \pm 17.7 days [median: 22 days, range 8–69]. In 5 patients (7.7%) postoperative lavage had to be continued on an outpatient basis after discharge from hospital.

Predictors of stage of empyema

Younger aged patients presented later in the course of the disease. The duration of preoperative antimicrobial therapy was not significantly different for stages I and II but for stages I and III, and for stages II and III. ► Fig. 3 shows the duration of preoperative antibiotic treatment in relation to the stage of empyema.

Predictors of 30-day and in-hospital mortality

Patients aged \geq 65 years had a significantly increased 30-day mortality, and there was a clear trend also for in-hospital mortality. Cardiac, renal and vascular diseases increased both 30-day and in-hospital mortality. An overview is presented in **> Tab.4**.

Finally, the presence of 3 comorbidities had a significant impact on 30-day mortality (p=0.001, OR 7.01, 95% CI 1.99 to 24.73).

The staging of empyema itself had no significant effect on 30-day mortality in stages I and II (p>0.05; stage I: OR 1.74, 95% CI 0.45 to 6.71; stage II: OR 2.13, 95% CI 0.56 to 8.07), whereas stage III was associated with a slightly lower mortality (OR 0.94, 95% CI 0.90 to 0.97).

Discussion

The main results of the present study were the following: 1) the initial success rate of treatment of patients with pleural empyema by a VATS-approach was high across all stages, albeit decreasing in stages II and III; 2) conversion was only necessary in stage III and reached 9.2%; 3) revision operations were necessary in 19.7% and 27.7% of patients with stage II and III, respectively; 4) most referrals of empyemas took place at the weekend, in particular on fridays; 5) younger ages were prone to late stages of effusions; 6) anaerobes and streptococci were the most frequent pathogens found in pleural effusions or tissue homogenates; 7) 30-day and in-hospital mortality was low, with age, cardiac, renal and vascular comorbidities as well as high comorbid load (3 comorbidities) being predictors.

Using video-assisted thoracoscopy for the treatment of pleural empyema in stage II and III is a widely accepted approach. The objective of the treatment of pleural empyema is the removal of all infectious tissue from pleural cavity, achieve complete re-expansion of the lung and avoid restrictive impairment after convalescence [5]. The feasibility of minimal invasive management is demonstrated in several studies and many additional benefits are reported [6,7]. VATS is shown to be su-

▶ Table 4 Predictors of 30-day and in-hospital mortality.

	30-day mortality			In-hospital mortality				
	р	OR	95% Confidence Intervall (CI)	р	OR	95% Confidence Intervall (CI)		
Age	0.004	5.85	1.54-22.21	0.063	2.35	0.934-5.91		
Comorbidities								
Cardiac	0.008	4.84	1.37-17.13	0.010	3.61	1.29-10.14		
 Pulmonary 	0.204	2.24	0.63 - 7.97	0.303	1.78	0.59-5.38		
 Hepatic 	0.433	0.95	0.92-0.98	0.160	3.01	0.60–15.11		
 Renal 	0.000	8.15	2.34-28.43	0.000	7.19	2.49-20.73		
Extrapulmonary tumor	0.119	2.89	0.72-11.56	0.016	3.73	1.20-11.65		
 Alcohol/drug abuse 	0.188	0.95	0.92-0.98	0.943	0.95	0.20-4.38		
 Diabetes mellitus 	0.408	0.43	0.05-3.41	0.518	0.61	0.13-2.78		
CNS	0.275	2.12	0.54-8.39	0.074	2.69	0.88-8.24		
 Vascular disease 	0.001	8.10	1.86-35.25	0.000	12.10	3.40-43.14		
 Infections 	0.266	0.95	0.92-0.98	0.629	0.60	0.08-4.79		

perior compared to thoracotomy with regard to operation time, length of hospital stay, postoperative pain and greater satisfaction with postoperative wound appearance.

The BTS and EACTS recommend antibiotic treatment and insertion of a chest tube in patients suffering from empyema stage I to evacuate parapneumonic effusion. The success rate of chest tube insertion as first-line treatment is reported to range from 67 to 74%, but several series report of success rate between 35% and 64% [1,8]. In our group, 38 patients underwent VATS for first-line treatment. Only patients in unstable conditions were treated with VATS after insertion of chest tube. The success rate in our cohort was 97.6% with a mean length of treatment (LOT) of 8 days. Wozniak et al. present a population of 104 patients with empyema stage I and stage II (stage III empyema was excluded from the study) from different causes [9]. Regardless to the stage of the empyema, the choice of first intervention and its success had an impact on the outcome. Simple drainage procedures were less successful even in lower stages (38% to 49%) while operative procedures had a success rate of more than 80%. The mean length of hospital stay was 17.3 days ± 1.5 days in case of success but increased to 22.6 days ± 3.1 days, if the first intervention was not successful.

The success rate of surgery was 80.3% in empyema stage II and 63.1% in empyema stage III. These results compare favourably with those reported in the literature, ranging from 91 - 100% in stage II to 82 - 93% in stage III [10].

The overall conversion rate in our cohort was 2.4%. There were no conversions to thoracotomy in patients with empyema in stage I or II; in stage III conversions were necessary in 9.2% of patients. Chan et al. presented a population of 77 patients with empyema from different causes [11]. In their survey 41 pa-

tients were treated by VATS and 36 patients were treated by thoracotomy. There was no conversion to thoracotomy in the VATS-group. Although 75% of these patients had an empyema stage III (according to the ATS-classification) the success rate in this subgroup was 100%. Nevertheless, the conversion rate in literature is stated to range between 8.2% and 19% [12].

In order to prevent a higher empyema stage associated with impaired outcomes, early suspicion and diagnosis is crucial. Our analysis of admission patterns according to weekdays showed that most patients were admitted on weekends, in particular on fridays, obviously hinting at a detection gap of empyemas during working days. Another potential delay may result in younger ages. Age is a known risk factor for empyema [13]. In our own cohort we found higher stages of empyema in younger patients and vice versa. It appears that younger patients consult their physician later in the course of their disease because they are able to compensate their physical impairments. Thus, an increased level of suspicion in patient management with pneumonia and pleural effusions as well as in younger patients may contribute to better early detection of empyema.

Overall, in 41.1% of the patients a bacterial pathogen could be isolated from intrapleural samples. Anaerobes and streptococci were the most frequent pathogens in pleural fluids and/ or tissue homogenates. These results are in line with the literature [14-16]. In 35.5% of the patients, the samples of bronchial secretions revealed a pathogen. However, these cultures mirror effects of prolonged antibiotic treatment and cannot be regarded as underlying pathogens in many cases. Other authors were able to verify the presence of bacteria in up to 60% of their patients [17, 18]. Our yield was slightly lower, most probably due to antibiotic pretreatment. Mortality in different publications addressing management of pleural empyema is stated to range between 0% and 6.7% [19,20]. In our cohort the overall 30-day mortality was 4.8%. Risk factors were an age above 65 years, cardiac, renal, and vascular comorbidities as well as multimorbidity. Other surveys published similar results regarding risk factors for increased morbidity [20]. The increased morbidity in our patients in pleural empyema stage III was significant. Many of these patients exerted several risk factors, like age above 65 and multimorbidity.

In conclusion, our data confirm that VATS is a successful management approach of parapneumonic empyema, associated with a low revision and conversion rate. However, in view of a considerable mortality rate, a higher index of suspicion and early detection of empyemas remain crucial in order to improve overall outcomes.

Conflict of interest

There are no conflicts of interest to declare.

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